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13. ABSTRACT (Maximum 200 Words)

Prostate cancer kills more Puerto Rican men than cancers of the lung, trachea and bronchus. Physical activity has an inconsistent relationship with prostate cancer. It is not clear what the relationship between body habitus and physical activity is among non-Whites population. The underlying hypothesis of this epidemiological research is that excess body adiposity and sedentary lifestyles are independent risk factors for prostate cancer mortality in Puerto Rican men. The specific aims of this proposal are (1) to investigate the association between anthropometric measurements or changes in body weight and prostate cancer mortality, and (2) to study the relationship between physical activity and prostate cancer mortality. This study uses an observational longitudinal design with a random sample of 9,824 Puerto Rican men aged 35-79 years at baseline (1964) who were part of the Puerto Rico Heart Health Program (PRHHP). Using a survival analysis approach and a total follow-up time of approximately 35 years we plan to examine the relationship of the above risk factors with prostate cancer mortality. There continues to be health disparities in prostate cancer incidence and mortality in minorities and our findings will improve our knowledge of the relationship between prostate cancer and other lifestyles.

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Annual Report
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Title: Prostate Cancer Mortality in Puerto Rican Men: The effect of body habitus and physical activity

INTRODUCTION:

Subject: Prostate cancer kills more Puerto Rican men than the combined cancer mortality rates of the lung, trachea and bronchus. The most extensively studied risk factors for prostate cancer include age, race/ethnicity, family history, diet, androgen metabolism, alcohol consumption, obesity, physical activity and smoking. Of these, age, race and family history are well documented but poorly understood risk factors. The fact that prostate cancer rates change in migrant populations and vary dramatically in ethnically similar populations residing in different geographic locations strongly suggest that environmental factors can greatly influence the risk of this cancer. **Purpose:** The purpose of this investigation is therefore, to study the relationship of physical activity and body habitus with prostate cancer mortality among Puerto Rican men. This study uses an observational longitudinal design with a random sample of 9,824 Puerto Rican men aged 35-79 years at baseline (1964) who were part of the Puerto Rico Heart Health Program (PRHHP). The Puerto Rico Heart Health Program provides a unique epidemiological cohort of men who took part in multiple examinations including extensive information on lifestyle, diet, body composition, exercise, and smoking habits. Survival analyses will be used to study the relationship between prostate cancer mortality and physical inactivity and obesity with approximately 35 years of follow up data. **Scope of the research:** This research is to generate new knowledge of how sedentary lifestyles or excess body weight are related to prostate cancer mortality, and to increase our knowledge of prostate cancer in a population where prostate cancer is the number one killer. Additionally, once prostate cancer mortality is identified, other exposures such as diet, smoking and alcohol intake can also be studied.

BODY:

Below is an itemized list of activities that have been conducted during year 3 of the research and our progress in completing these tasks. Primarily there are two papers that have been submitted for review into the International Journal of Epidemiology and

the American Journal of Epidemiology. The manuscript "Physical Inactivity is not a predictor of prostate cancer mortality in Puerto Rican men" and is being submitted to the International Journal of Epidemiology. The second manuscript on "Body mass index and its relationship to prostate cancer mortality in US Whites and Blacks: the feasibility of a J-shaped curve" is to be submitted to the American Journal of Epidemiology.

While we are presenting some tables and figures in the body of the report, the reviewers can find a comprehensive discussion of the findings in the appended two manuscripts. As noticed from the titles of our papers, we found a null relationship between physical activity and prostate cancer, while the association between BMI and prostate cancer seems to be J-shaped.

We encountered some problems in accomplishing some of our tasks. From our report in year 02 we further validated our prostate cancer mortality cases and found that the total number of prostate cancer cases went up from 74 to 88. The increase is explained by further validating ICD codes in the databases and by purchasing the death certificates of the cases. The 74 prostate cancer cases where those with ICD-9 and excluded prostate cancer cases with ICD-10. Our revised estimates include ICD-9 and ICD-10 prostate cancer cases. We carefully analyzed our data to look at body weight, weight gain, and relative body weight as they relate to prostate cancer mortality. Unfortunately we were limited in the lower than expected number of cases (N=88) to be able to test the J-shaped curve hypothesis and prostate cancer mortality.

Manuscript 1:

To better understand the relationship between BMI and prostate cancer, we therefore examined another dataset with a large number of prostate cancer cases that included minority populations from the National Health Interview Survey (NHIS). We were able to examine a J-shaped correlation matrix between BMI and prostate cancer among Whites and Blacks. The NHIS is a national representative sample of the US population conducted by the Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics. Participants are sample yearly and follow up with mortality using the National Death Index within the CDC. Table 1 is a descriptive characterization of US Blacks and Whites that we used as our analytic sample obtained from the National Health Interview Survey.

Table 1. Number, Average BMI, Average Income, and Average Education by Race and age groups for Prostate Deaths, Other Deaths, and the Living

	Prostate Deaths				Other Deaths				Living			
	No.	BMI	Income	Educ	No.	BMI	Income	Educ	No.	BMI	Income	Educ
Blacks												
40 – 49	1	32.4	.	12	399	26.9	22811	11.3	6082	26.7	31748	12.2
50 – 59	20	28.5	22742	10.3	604	26.5	22724	10.1	4107	27.1	29842	11
60 – 69	62	26.6	19039	9.8	1003	25.9	17926	8.8	3037	26.7	22309	9.7
70 – 79	77	26.2	15511	7.5	847	25	14821	7.8	1378	26	16866	8.6
80 +	35	24.1	14716	6.8	438	24.1	12305	6.3	313	24.6	13323	6.8
Whites												
40 – 49	11	27.9	42136	13.4	1337	26.9	35086	12.5	44712	26.6	43223	13.7
50 – 59	24	26.5	44048	12.8	2631	26.6	33621	11.8	30503	26.8	42278	13
60 – 69	166	26.7	33686	11.8	5472	26	27213	11.4	24117	26.4	33235	12.3
70 – 79	287	25.1	24804	11.4	6722	25.1	22486	10.8	12302	25.6	25964	11.6

80 +	167	23.7	20676	10.1	3912	23.6	20736	10.1	2697	24.6	22359	10.8

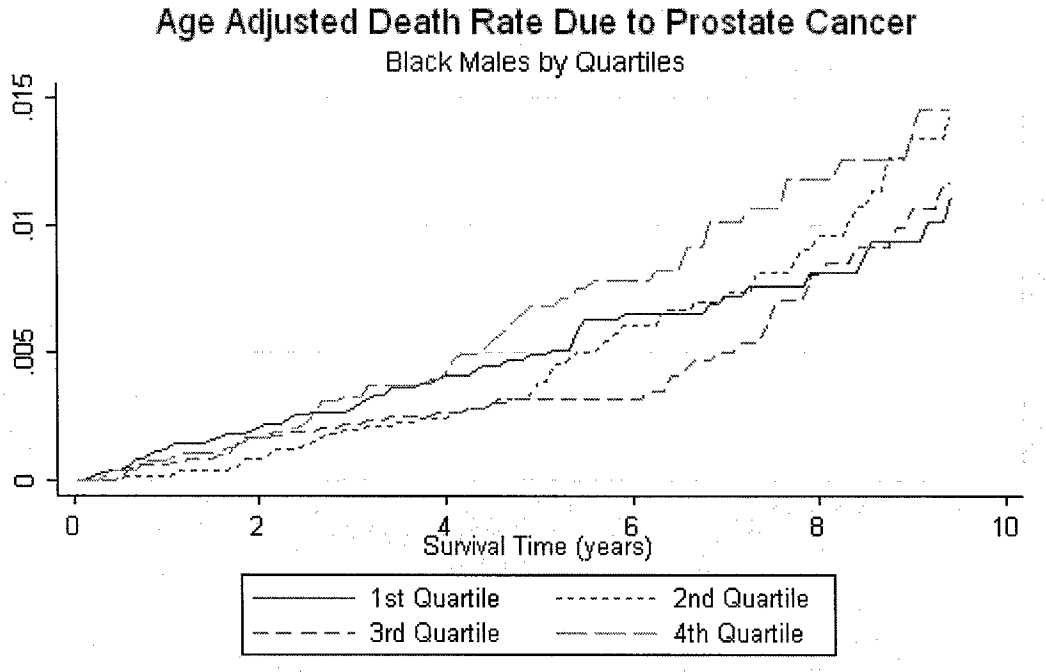

Figure 1

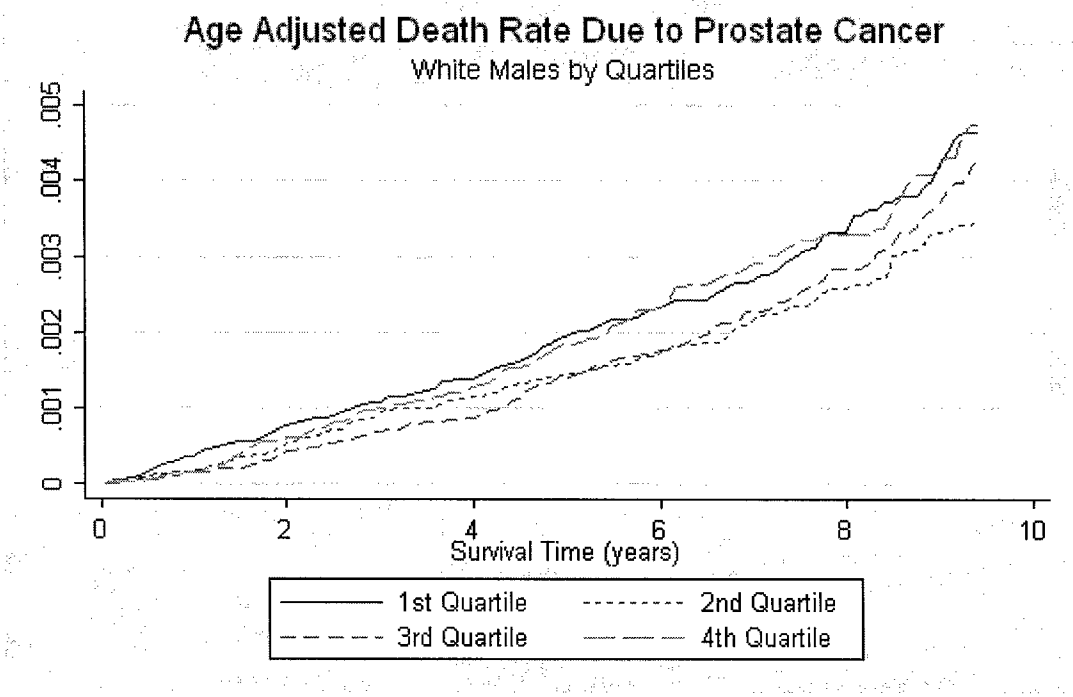

Figure 2

Figures 1 and 2 above show a survival curve of prostate cancer mortality according to different BMI quartiles among Blacks and Whites using a national representative sample dataset from the National Health Interview Survey.

Manuscript 2:

In our manuscript examining the relationship between physical activity and prostate cancer we found no relationship between quartiles of physical activity, participation in vigorous physical activity and engaging in no physical activity for 12 or more hours a day. We found that none of this physical activity measures were related to prostate cancer mortality.

Table 1 list the distribution of prostate cancer mortality cases, non-prostate cancer cases, and those who are alive at time of follow up.

Table 1. Description of participants in the Puerto Rico Heart Health Program according to prostate cancer mortality status and distribution by selected characteristics.

	N = 9,824	All	Non-Prostate Cancer Death N = 3,123	Prostate Cancer Death N = 88	Alive N = 6,613
Age, in years					
35 – 44 years	349	3.6%	2.1%	1.1%	4.3%
45 – 54 years	4931	50.2%	42.3%	48.9%	53.9%
55 – 64 years	3862	39.3%	45.3%	45.5%	36.4%
65 years and older	682	6.9%	10.3%	4.6%	5.4%
Education					
No formal schooling	995	10.2%	9.7%	5.7%	10.4%
Grades 1 to 4	3455	35.2%	32.0%	19.3%	37.0%
Grades 5 to 8	2819	28.8%	29.5%	42.1%	28.2%
Attended/completed HS	1726	17.6%	19.1%	14.8%	17.0%
Attended/completed College	808	8.2%	9.7%	18.2%	7.4%
BMI					
Underweight	324	3.3%	4.1%	2.3%	2.9%
Normal weight	4623	47.1%	43.2%	42.1%	49.0%
Overweight	3689	37.5%	39.0%	44.3%	36.8%
Obese	1188	12.1%	13.8%	11.4%	11.3%
Smoking					
Nonsmokers	3329	33.9%	32.3%	29.6%	34.7%
Previous smokers	2205	22.5%	22.7%	25.0%	22.3%
Current smoker	4282	43.6%	45.0%	45.5%	43.0%
Living					
Rural	2981	30.3%	24.6%	20.5%	33.2%
Urban	6843	69.7%	75.4%	79.6%	66.8%
Physical Activity					
Quartile 1 (Low)	2687	27.4%	35.1%	23.9%	23.7%
Quartile 2	2427	24.7%	25.0%	26.1%	24.5%
Quartile 3	2291	23.3%	22.1%	26.1%	24.0%
Quartile 4 (High)	2419	24.6%	17.8%	23.9%	27.9%

Table 2 shows the age and BMI adjusted odds ratio of prostate cancer mortality.

Table 2 Odds ratio of physical activity and prostate cancer mortality Among Puerto Rican Men, after adjustment for age and body mass index			
Quartiles of physical activity	Odds Ratios	95% Confidence Intervals	P-value
Quartile 1 (Low-inactive)	1.0	Reference	
Quartile 2	1.23	0.68, 2.22	0.50
Quartile 3	1.33	0.74, 2.39	0.35
Quartile 4 (High)	1.21	0.65, 2.25	0.55

We found no relationship between physical activity and prostate cancer mortality. Quartile 1 includes the most inactive category at baseline. More active groups did not have significantly lower or higher risks of prostate cancer mortality. Adjustment for other confounders did not alter this relationship. Participation in vigorous leisure time physical activity 1 hour or more a day, was not protective against prostate cancer either.

Key research accomplishments:

1. Our results show that physical activity is not related to prostate cancer mortality in this group of Puerto Rican men. This is consistent with findings from other longitudinal studies. However, other studies have found it to be protective.
2. We applied a Cox proportional hazard modeling to assess the possibility that the relationship between BMI and prostate cancer is J-shaped rather than linear. Our findings showed a significant increase in prostate cancer mortality for Whites and Blacks.
3. Our manuscript on physical activity and prostate cancer in Puerto Rican men will be the first paper to assess prostate cancer mortality among Hispanics.
4. The manuscript on BMI and prostate cancer mortality is the first paper to attempt to fit a J-shaped curve in a White and Black population.
5. We published a paper to examine pulse pressure as an independent risk factor for cardiovascular disease – see appendix. We propose to assess how pulse pressure which is a surrogate of cardiovascular stiffness relates to prostate cancer mortality as has been reported by others
6. Lower Urinary Tract Symptoms (LUTS) has been associated with prostate hyperplasia and prostate cancer. We examined the cross sectional relationship of lifestyle factors, including physical activity and LUTS in Blacks, Whites and Hispanic men from the National Health and Nutrition Examination Survey – see appendix. This paper has been accepted for publication in the British Journal of Urology.

Reportable outcomes:

Manuscripts:

1. Physical inactivity is not a predictor of prostate cancer in Puerto Rican men.
2. Body mass index J-shaped relationship with prostate cancer in both Whites and Blacks
3. Pulse pressure and cardiovascular mortality in PR men.

4. LUTS from NHANES III

Abstracts:

1. American College of Sports Medicine

Conclusions:

Importance of completed research:

The importance of the completed research is that our findings support the hypothesis that physical activity is not related to prostate cancer. While the relationship between physical activity and prostate cancer remains inconclusive, our research lends evidence of a null relationship.

Changes on future work;

Our study on the relationship of body habitus and prostate cancer shows that BMI is not linearly related to prostate cancer mortality. Our findings are the first one to examine a J-shaped relationship, in both Whites and Blacks. Therefore, future work and already published studies – should carefully examine whether a J-shaped curved is a better predictor of prostate cancer mortality.

So what section:

While our results showed that physical activity is not related to prostate cancer mortality, other studies have found an inverse relationship. Even when we limit the evidence to longitudinal studies, the findings remain inconclusive. Future studies, therefore, should aim at better characterizing physical activity into primarily aerobic or anaerobic. The effect of aerobic or anaerobic physical activities on circulating testosterone may provide additional insights on how exercise relates to prostate cancer.

Additionally, our original analysis on the relationship between BMI and prostate cancer in Puerto Rican men showed no significant relationship. In order to have a larger sample size to assess other types of relationships, we studied data from the National Health Interview Survey which contain over 600 prostate cancer cases and also had a substantial number of Whites and Blacks. With a larger number of cases we were able to test the hypothesis that the relationship between BMI and prostate cancer was not linear, but that a J-shaped curve was a better predictor of prostate cancer mortality. Thus, future studies – or already published studies - should attempt to model this J-shaped relationship to better characterize the role of BMI on prostate cancer risk. Moreover, this new finding could provide some evidence of a minimum and maximum threshold for which a BMI level may increase the risk for prostate cancer.

Physical Inactivity is not a predictor of prostate cancer in Puerto Rican Men

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Introduction:

Second to lung cancer, prostate cancer kills more men than any other cancer in the United States. This particular high cancer mortality is also observed among other Western societies(1). The incidence and mortality from cancer among African American men is considered one of the highest in the world (2). Although microscopic (latent) prostate tumors in most populations are similar, striking differences in the incidence rates among racial/ethnic groups exist. During the years of 1988 and 1992, the highest reported rates (age-adjusted world standard), exceeding 30,000 per 100,000 man years, were observed among US blacks. Rates in Black Caribbean men, especially from Jamaica, are also among the highest in the world. In Europe, incidence rates were higher in France, but notably lower in the United Kingdom, Italy, and Spain, yet prostate cancer mortality was similar in Italy and Spain (11.2/100,000 and 13.5/100,000, respectively. Prostate cancer mortality among all Hispanics in the US are considered lower than those of non-Hispanic whites, however, differences among Hispanic subgroups support an increased burden of prostate cancer mortality among Puerto Ricans and other Caribbean men. Despite the increased mortality of prostate cancer among men, and minority men, there is little knowledge about lifestyle changes that can modify the risk. (2-13).

Prostate cancer rates in the Commonwealth of Puerto Rico are not very dissimilar to those observed in the United States. For example, the age-adjusted prostate cancer mortality rates among men from Puerto Rico and the United States are 16.1/100,000 and

15.7/100,000 respectively. However, prostate cancer kills more Puerto Rican men in Puerto Rico than any other cancer, including lung cancer. Puerto Ricans in the United States are the second largest Hispanic subgroup and have prostate cancer mortality rates lower than those observed in Puerto Rico, but higher than other Hispanic subgroups such as Mexican Americans or Cuban Americans(7-9;12). The fact that prostate cancer rates change in migrant populations and vary dramatically in ethnically similar populations residing in different geographic locations strongly suggest that environmental factors can greatly influence the risk of this cancer(14).

One important lifestyle that has been associated with prostate cancer is physical activity. The relationship between physical activity and prostate appears to be inconsistent. While the majority of the studies show a small protective benefit, there are substantial reports showing no relationship or an increased risk with physical activity. Moreover, the relationship between physical activity and prostate cancer among US minority men has not been well characterized (15-23) .

The purpose of this study is to examine the relationship between physical activity and prostate cancer mortality in a cohort of Puerto Rican men who took part in the Puerto Rico Heart Health Program.

Methods:

Study population:

The Puerto Rico Heart Health Program is a prospective cohort study designed to examine morbidity and mortality from coronary heart disease in urban and rural Puerto Rican men (24-27). Briefly, the original sampling was designed to recruit men aged 45 to 64 years who were free from coronary heart disease at time of first examination in 1965. These men were sampled from 3 urban areas and 4 rural areas in the northeast part of Puerto Rico by the personnel who participated in the United States decennial census (26). All of these men were encouraged to attend the baseline examination, and an 80% response rate was achieved. The original sample of the cohort consisted of men ages 45 to 64 years of age. Other participants aged 35-44 years and 65 to 79 years, who had been inappropriately included in the enumeration, were also included in this study. Thus, the total number of examined participants used in this analysis includes 9,824 men between the ages of 35 to 79 years.

All men completed an extensive self-report of demographic characteristics, personal and family health history, and health habits, including education, occupation, income, a history of smoking, and place of residence among other characteristics.

Assessment of physical activity and other characteristics

During the first examination each participant provided sociodemographic information and a complete medical history with a physical examination that included laboratory determination, and a resting 12-lead electrocardiogram was conducted. At this first examination complete physical activity status was assessed using the Framingham

Physical Activity Index (25;28). This questionnaire assesses occupational, leisure-time and other physical activities, measured as usual activity over the course of a 24-hour day, and was interviewer-administered. Usual physical activity was determined by a review of the number of hours spent at various activities. For analysis, the number of hours at each activity was converted to an index of usual daily energy expenditure. This was accomplished by grading activities into different categories using estimated oxygen consumption per hour for each activity or metabolic equivalents (METs). One MET is equivalent to energy expenditure at rest, approximately 3.5 ml of O_2 per kilogram of body weight per minute. The usual activities were classified as sedentary (MET=1.0), slight (MET=1.1-2.3), slightly moderate to moderate (MET=2.4-4.9) and strenuous (MET=5.0+). The product of this grade and duration in hours gave a score of a physical activity index. A score of 24 meant the individual slept or reclined for 24 hours in a day. Higher scores indicated either strenuous activity for short periods or moderate activity for a longer time. Estimates of consistency of administration between the first test and 2- to 3-year post-test in this group of Puerto Rico men provided Pearson correlation coefficients of .30 to .59 using the Framingham Physical Activity Index (25;29).

We stratified our analytic sample by quartiles of physical activity. The physical activity index ranged from 24 to 71. We further examined patterns of physical activity within quartile by hours spent doing no activity such as sleeping or resting; sedentary or very light activities such as sitting; light activities such as walking at level; moderate physical activity such as brisk walking, climbing stairs or walking uphill; and vigorous physical activity such as cutting sugar cane or other strenuous activities. The cutoff point for quartile 1 was a physical activity index of 27 or less and represents the group that is

most inactive. To assure quartile 1 reflects those who are sedentary, we reclassified 18 participants (out of 2401) in quartile 1 who reported participating in moderate physical activities into quartile 2 (N=2277). Thus, quartile 1 of physical activity includes participants who engaged in no physical activities, sedentary activities or light physical activities. The range of physical activity index for quartile 2 was greater than 27 but less than 30, for quartile 3 the range was greater than or equal to 30 but less than 37 (N=2171), and for quartile 4 scores were greater than or equal to 37 (N=2287).

Obesity classification:

We used the guidelines released by the National Heart, Lung, and Blood Institute; National Obesity Education Initiative to classify our participants based on body mass index (BMI) (30). Briefly, underweight individuals are those whose BMI is less than 18.5; normal or healthy weight represent persons with BMI between 18.5 and 24.9; overweight are persons with BMI between 25 and 29.9; and obesity of stages 1, 2, and 3 represent BMI of 30-34.9, 35-39.9, and 40 or more, respectively. We collapsed stages 1, 2 and 3 into one category because few of our participants had BMI greater than 35 (stage 2, N=96, stage 3, N=20).

Other covariates:

Education level was determined from history by ascertaining the highest grade completed in school. For our analysis, participants were grouped into five categories: No formal schooling, and those who attended or completed grades 1-4, grades 5-8, high school, or college. The detailed smoking history provided the basis to classify

participants into nonsmokers, previous smokers, and smokers for the multivariate analysis. Rural-urban residence was determined based on place of residence at baseline. The characterization of the rural area was composed primarily of small farms located on very hilly terrain while the urban area consisted of a more dense cluster of houses, many of whose residents worked in the business and industry around San Juan.

Ascertainment of fatal prostate cancer

We conducted a passive follow up by matching participants in the Puerto Rico Heart Health Program with electronic files from the Puerto Rico Cancer Registry and Puerto Rico Vital Statistics Registry. We matched the cases based on a full match on first name, last names (father last names and mother last names) date of birth (month, day, year), place of birth, and gender. Validity of the matched cases were conducted by obtaining copies of the death certificate and verification of prostate cancer as a cause of death. Eighty-seven of the 88 cases resulted on death certificates had a prostate cancer diagnosis at time of death.

Statistical Analysis:

The study uses prostate cancer mortality as the outcome variable. The multivariate logistic function model was used to analyze relationships between known risk factors and prostate cancer mortality. We examined the potential contribution of the following variables in the model: age (years), education (no formal schooling, grades 1-4, grades 5-8, attended or completed high school, attended or completed college), body weight classification (underweight, healthy weight, overweight, obesity), baseline

smoking status (non-smokers, former smokers, current smokers), and urban-rural residence (urban, rural) (28;31-33).

Results:

Table 1 shows that there was not an appreciable difference between prostate cancer cases, non-prostate cancer deaths and those who were alive after almost 36 years of follow up. A few noticeable differences were that the prostate cancer cases seems to be higher educated with 18 percent having attended or completed College compared with less than 10 percent among those who were alive or died of other causes. The percent distribution of prostate cancer cases among the different quartiles of physical activity ranged from 23.9 percent to 26.9 percent, showing little variability. In contrast, among those who died of non-prostate cancer causes there was a higher percentage who were physically inactive (quartile 1, 35.1%) compared with those who were highly active (quartile 4, 17.8%).

Insert Table 1 Here

After adjustment for age and BMI, we found that physical activity was not protective against prostate cancer mortality in this group of Puerto Rican men. Adjustments for other confounder outlined in Table 1 did not modify the relationship, and were not significantly related to prostate cancer either.

Insert Table 2 Here

Discussion

In our review of the literature of longitudinal studies that examined the role of physical activity on prostate cancer risk we found inconclusive results. While some longitudinal studies have found a protective effect of physical activity on prostate cancer risk(18;34-40), other longitudinal studies found no association or positive association between physical activity and prostate cancer (21;41-45). It is not surprising the several comprehensive reviews of the literature that included longitudinal and case-control studies concluded that the relationship between physical activity and prostate cancer remains inconsistent (22;46). Our results are in accordance with those that found no association between physical activity and prostate cancer. We did not observe a dose-response trend either and adjustment for age, BMI, smoking or education did not change the association.

Our results also showed excess non prostate cancer mortality among the inactive, and this may be due to cardiovascular mortality and its established link with physical inactivity. We also found that prostate cancer cases had substantially higher educational attainment compared to those who were alive or died of other causes. This is very consistent with other hormonal related cancers such as breast cancer where education has been found to be positively related.

The majority of the studies above were conducted in men of European ancestry. One study was from Shanghai, another from Hawaii, and another had data on African Americans (34;35;47). Severson et al (40) used the same physical activity index from the Framingham study and heart rate in a cohort of 7,925 Japanese men in Hawaii aged 46-65

years and prostate cancer incidence was the outcome of interest. After adjustment for age and BMI they found no association when comparing the most active relative to the least active men, no protective effect of occupational physical activity and heart rate was not related to prostate cancer incidence either. Our study used the same Framingham Physical Activity questionnaire and the results also point toward a null relationship.

In summary physical inactivity was not a risk factor for fatal prostate cancer in this group of Puerto Rican men. While most of the literature that have reviewed the relationship between prostate cancer and physical activity have been among European whites, our study is the first to examine this relationship longitudinally in a well characterized subgroup of Hispanics.

Table 1. Description of participants in the Puerto Rico Heart Health Program according to prostate cancer mortality status and distribution by selected characteristics.					
	N = 9,824	All	Non-Prostate Cancer Death N = 3,123	Prostate Cancer Death N = 88	Alive N = 6,613
Age, in years					
35 – 44 years	349	3.6%	2.1%	1.1%	4.3%
45 – 54 years	4931	50.2%	42.3%	48.9%	53.9%
55 – 64 years	3862	39.3%	45.3%	45.5%	36.4%
65 years and older	682	6.9%	10.3%	4.6%	5.4%
Education					
No formal schooling	995	10.2%	9.7%	5.7%	10.4%
Grades 1 to 4	3455	35.2%	32.0%	19.3%	37.0%
Grades 5 to 8	2819	28.8%	29.5%	42.1%	28.2%
Attended/completed HS	1726	17.6%	19.1%	14.8%	17.0%
Attended/completed College	808	8.2%	9.7%	18.2%	7.4%
BMI					
Underweight	324	3.3%	4.1%	2.3%	2.9%
Normal weight	4623	47.1%	43.2%	42.1%	49.0%
Overweight	3689	37.5%	39.0%	44.3%	36.8%
Obese	1188	12.1%	13.8%	11.4%	11.3%
Smoking					
Nonsmokers	3329	33.9%	32.3%	29.6%	34.7%
Previous smokers	2205	22.5%	22.7%	25.0%	22.3%
Current smoker	4282	43.6%	45.0%	45.5%	43.0%
Living					
Rural	2981	30.3%	24.6%	20.5%	33.2%
Urban	6843	69.7%	75.4%	79.6%	66.8%
Physical Activity					
Quartile 1 (Low)	2687	27.4%	35.1%	23.9%	23.7%
Quartile 2	2427	24.7%	25.0%	26.1%	24.5%
Quartile 3	2291	23.3%	22.1%	26.1%	24.0%
Quartile 4 (High)	2419	24.6%	17.8%	23.9%	27.9%

Table 2 Odds ratio of physical activity and prostate cancer mortality Among Puerto Rican Men, after adjustment for age and body mass index			
Quartiles of physical activity	Odds Ratios	95% Confidence Intervals	P-value
Quartile 1 (Low-inactive)	1.0	Reference	
Quartile 2	1.23	0.68, 2.22	0.50
Quartile 3	1.33	0.74, 2.39	0.35
Quartile 4 (High)	1.21	0.65, 2.25	0.55

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The Feasibility of a J-shaped Curve when Body Mass Index is Used to Predict the Risk of Mortality from Prostate Cancer

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A Introduction

Researchers have conducted cohort and case-control studies involving diverse populations to determine the relationship between prostate cancer and obesity, usually measured in terms of Body Mass Index (BMI), defined as $BMI = \frac{kg}{m^2}$. We will use the National Health Information Survey (NHIS) data to examine the relationship between BMI and risk of prostate cancer for Black and White males. We will explore the feasibility of using a J-shaped risk curve to determine the effect of this approach on risk. We will try to find the BMI value that minimizes risk. And, we will try to shed some light on why past studies have produced varied and sometimes seemingly contradictory results.

A number of studies have been conducted to examine the relationship between BMI and risk of developing prostate cancer that show either no relationship or an inverse relationship between these two factors. Lee, Sesso, and Paffenbarger [1] examined the relationship between physical activity and prostate-cancer risk for men enrolled in the Harvard Alumni Study. During the 6-year followup, 439 of the 8,922 participants developed prostate cancer. The analysis showed no evidence that either physical activity or body weight played a role in prostate-cancer etiology. Nilson and Vatten [2] completed a 12-year followup of 22,248 Norwegian men and also found no relation between BMI and prostate cancer. Giovannucci and coworkers [3] studied 2,896 incidents of prostate cancer from the Health Professionals Followup Study and concluded that no relationship exists between BMI and prostate cancer among older males(age $\geq$ 60 years). They found, however, that younger males with lower BMIs exhibited a higher risk of prostate cancer than did their counterparts with higher BMIs, showing an inverse relationship between BMI and prostate-cancer risk for younger males.

The following studies show a positive relationship between BMI and prostate cancer. Calle and co-workers [4] observed 404,576 male volunteers who were free of cancer at enrollment in 1982. During 16 years of followup, they reported significant trends relating higher BMI with higher risk of death from prostate cancer. Rodriguez and co-workers [5] examined BMI, height, and prostate-cancer mortality in two large cohorts of men selected from the Cancer Prevention Study I (CPS-I), who were enrolled in 1959 and followed through 1972, and from the Cancer Prevention Study II (CPS-II), who were enrolled in 1982 and followed through 1996. After exclusions, 1,590 prostate-cancer deaths remained among 381,638 men in CPS-I and 3,622 deaths, among 434,630 men in CPS-II. The investigators used Cox proportional hazards modeling to compute rate ratios (RR) and adjust for confounders. They found prostate-cancer mortality rates to be sig-

nificantly higher among obese men (BMI $\geq$ 30).

The above studies present a representative sample of the research that has been conducted on this subject. There are additional studies [6, 7, 8, 9, 10] that conclude the relationship between BMI and prostate cancer to be positive and also a number of further studies [11, 12, 13] that find no relationship exists.

In 1997, Durazo and coworkers showed that the relationship between BMI and overall death can be modeled effectively using a J-shaped risk curve [14]. To our knowledge, no study has considered the use of a J-shaped curve to model the relationship between BMI and prostate cancer. Goetghebeur and Pocock [15] have suggested a protocol for determining when the use of a J-shaped curve is appropriate, along with a procedure for modeling when it is appropriate. For our analysis, we examine the risk of prostate cancer for Black and White males over 40 years of age using the NHIS survey data from 1986 to 1993, and explore the appropriateness of employing a J-shaped curve to explain the relationship between BMI and prostate cancer. We then compare the quality of models that assume a J-shaped curve to those that do not.

B Methods

B.1 Data

B.1.1 NHIS Survey Data

The NHIS is a continuing nationwide survey of the U.S. civilian, non-institutionalized population conducted through households. Each week a probability sample of households is interviewed by trained personnel from the U.S. Bureau of the Census to obtain information about the health and other characteristics for each member of the household. The average annual sample consists of 36,000 to 47,000 households, including 92,000 to 125,000 persons. The annual response rate is over 95 percent. Health and utilization variables include self reported age, height, weight, level of physical activity, family income, level of education, and self-assessed health status. To insure accuracy, a five-percent sample of all questionnaires is recoded and keyed by other coders. A 100 percent verification procedure is used if certain error tolerances are exceeded.

B.1.2 NHIS Mortality Followup

Beginning with survey year 1986, linkage information has been collected on NHIS respondents age 18 and over to allow for matching with other data systems, including the National Death Index (NDI). Linkage of NHIS respondents with NDI provides a longitudinal component to NHIS, which allows for the ascertainment of vital status. So far, multiple-cause-of death data is available for NHIS survey years 1986-94, with followup to December 31, 1997.

NCHS uses a modification of a probabilistic approach to classify the NHIS-NDI potential matches [16, 17]. They fit an NDI record to an NHIS record if there is correspondence on any of 12 criteria including: social security number, first name, middle initial, last name, father's surname, and birth month, day, and year. A matching score is assigned in accordance with the number and pattern of criteria successfully fitted. Five successive categories are formed based on these matching scores, the first classifying persons as deceased and the fifth, as still living. The remaining three classifications assign individuals as deceased with high degrees of probability. Our analysis uses only cases where the two highest scores are obtained, assuring a high degree of probability for the match.

More complete NHIS implementation procedures and linkage methodology are available at their website (www.cdc.gov/nchs/nhis.htm).

B.2 Statistical Methods

We began our analysis by tabulating basic statistics of interest in exploring the relationship between BMI and death from prostate cancer. These include the number of people classified by age and race who died from prostate cancer, who died from other causes, and who are still living, as well as the average BMI, average family income and average education for each of these sub-populations.

For a quick overview of the relationship between BMI and risk of prostate cancer, we graphed failure rates (calculated as 1-the Kaplan Meier survival rates) and cumulative incidence rates for the four quartiles of BMI. These curves were generated for Blacks and Whites and adjusted for age using a Cox proportional hazards model.

For this dataset, preliminary analysis showed that the lowest quartile and the highest quartile of values for BMI produce the greatest risk of prostate cancer. Hence, the risk of prostate cancer may follow a J-shaped curve as BMI increases among white males. Given that Durazo and coworkers showed that the overall death rate may follow a J-shaped curve [14], we wished to determine whether

low BMI values within this population were associated with general mortality or only with prostate-cancer mortality. To do this, we tabulated the overall death rates and the overall age-adjusted death rates for the four quartiles of BMI among white males.

Since the risk of prostate cancer as it relates to BMI among white males may follow a J-shaped curve, we were seeking the value of BMI that minimizes the risk of prostate-cancer death. In other words, we wanted to determine the point where the relationship between BMI and risk of prostate cancer changes from varying directly to varying inversely. To do this we followed the procedure outlined in [15].

To determine the relationship between BMI and prostate-cancer death, we fitted Cox proportional hazards models using BMI and age to predict survival time from prostate cancer for three distinct populations: the population consisting of all white males, the population of white males with BMI values above the change point determined by [15], and the population of white males with BMI values below the change point obtained by [15]. We then used likelihood ratio (LR) tests to determine the nature and the magnitude of the effect of BMI on risk of prostate cancer for these populations. These Cox models and LR tests were performed both without adjustment and adjusting for education, family income, physical activity, and height.

To obtain a sense of the overall relationship between BMI and mortality from all causes, we tabulated death rates and age adjusted death rates for the four quartiles of BMI.

High prostate cancer mortality rates among those with low BMI values may be a result of systemic weight loss in response to the illness. Correspondingly, we eliminated deaths that occurred within two years of the interview to determine whether this changed the relationship between low BMI and prostate cancer.

C Results

Table 1 shows a description of the number of cases, the average BMI, the average income and the average education for prostate cancer deaths, other deaths, and the living by age and race.

Figure 1 shows the rate of failure curves (calculated as 1-Kaplan Meier Survival Rate) adjusted for age for the four quartiles of BMI among black males. Quartile 1 represents the population with the lowest BMI values, quartile 4 represents that with the highest BMI values, and quartiles 2 and 3 represent the two

quarters of the population that lie between them. The figure reflects well what our various analyses and models also showed: Based on the data available in this study, we were unable to find a statistically significant link between BMI and the risk of prostate cancer among black males.

Figure 2 presents the same information for White males. If we observe only the 2nd, 3rd and 4th quartiles, they indicates that the risk of prostate cancer increases as BMI increases. If we observe only the 1st and 2nd quartiles, they indicate that the risk of prostate cancer decreases as BMI increases. This decreasing and then increasing risk as BMI increases seem to signify a J-shaped curve for the relationship between BMI and the risk of prostate cancer [15].

We graphed the estimated cumulative incidence, as well as the failure rate computed as (1-KM). As expected when competing risks are incorporated, the rates were slightly lower. However, there was no significant change in the nature of the curves (data not shown).

Since our data indicate that the relationship between BMI and risk of prostate cancer in white males may follow a J-shaped curve, we use the change point procedure outlined in [15] to obtain the value for BMI that should minimize the risk of prostate cancer. This procedure specifies that for values of BMI less than 24.8, BMI should vary inversely with the risk of prostate cancer, and for values of BMI greater than 24.8, BMI should vary directly with the risk of prostate cancer.

Finally, to obtain an overall sense of the relationship between BMI and risk of prostate cancer, we fitted Cox proportional hazards models with three populations: all white males, white males with BMI ≤ 24.8, and white males with BMI > 24.8. The following tabulations show the results of a Cox proportional hazards model where age and BMI were used to predict survival time for prostate cancer for all white males. The results are shown in Table 2. When all white males over 40 are included, the model shows that as BMI increases, the risk of prostate cancer declines. However, both the confidence interval on the BMI coefficient and the p-value on the LR test indicate that the overall inverse relationship determined by this model is not statistically significant. When only white males over 40 with BMI values greater than 24.8 are included, the model shows that as BMI increases, the risk of prostate cancer grows. Both the likelihood ratio test and the confidence interval on the BMI coefficient indicate that this result is statistically significant. When only white males over 40 with BMI values less than 24.8 are included, the model shows that as BMI increases, the risk of prostate cancer diminishes. Once again, both the likelihood ratio test and the confidence interval on the BMI coefficient indicate that this result is statistically significant. Hence, these models support a J-shaped curve to describe the relationship between BMI values and the

risk of prostate cancer as BMI increases.

When the Cox proportional hazards models were adjusted for education, family income, physical activity, and height, slight changes occurred in the results. The model of all white males over 40 shows an inverse correlation between BMI and the risk of prostate cancer with a very high p-value, indicating that a negligible relationship exists between BMI and risk of prostate cancer. When we assumed a J-shaped curve and sought the change point, we found that it occurred at a BMI value of 24.4 rather than 24.8. The population with BMI values less than or equal to 24.4 again showed an inverse relationship between BMI and risk of prostate cancer with a p-value of p=.0177. The population with BMI values greater than 24.4 showed a direct relationship between BMI and the risk of prostate cancer with a p-value of p=0.022. Hence, while the change in the value of the changepoint is statistically meaningful, the general nature of the relationship between BMI and the risk of prostate cancer does not change when adjusting for these variables.

Table 3 shows the overall and age-adjusted rates for all mortality causes for the four quartiles of BMI. This table indicates that the baseline risk of death from any cause is considerably higher for white males with low BMI values. Hence, while figure 2 suggests that risk of prostate cancer is higher for low BMI values, the association between all cause mortality and low BMI values may make the particular relationship between low BMI and death from prostate cancer more difficult to ascertain.

High mortality rates among those with low BMI values could be due to systemic weight loss in response to a disease. In this case, it is possible that removing imminent deaths would significantly change the nature of the models. However, when we removed all deaths within two years of the interview from our Cox Proportional Hazards Model, we found that there was still a statistically significant (p=0.02) inverse relationship between BMI values and the risk of prostate cancer for white males over 40 with BMI values less than 25.2.

D Discussion

The overall rate of death due to prostate cancer for males over 40 was greater than 1 percent among blacks and slightly less than 0.5 percent among whites. White victims of prostate cancer had considerably higher education and income and lower BMI values than black prostate cancer victims of the same agegroup. However, prostate cancer victims had incomes and BMI values very similar to their living counterparts of the same race and age group. The education of victims

of prostate cancer, however, tended to be lower than their living counterparts of the same race and age group.

In an attempt to better understand the relationship between BMI and prostate cancer, we applied the procedure outlined by [15] to check the appropriateness of a J-shaped curve associating BMI to the risk of prostate cancer for black males and found no evidence for a J-shaped curve in this population. We also applied a LR test with a Cox proportional hazards model using BMI to predict survival time among black males with age as a covariate and found insufficient evidence to assume a relationship between BMI and risk of prostate cancer among this population. Observing figure 1, at $t = 1$, the ordering of failure rates is Quartile 2 ¡ Quartile 3 ¡ Quartile 4 ¡ Quartile 1. At $t = 9$, the ordering of failure rates is Quartile 1¡ Quartile 3 ¡ Quartile 2 ¡ Quartile 4. Hence, our inability to discern a relationship between BMI and risk of prostate cancer for black males is not surprising given the data contained in this figure.

As stated above, we are not aware of prior discussions of the use Of a J-shape curve to describe prostate-cancer risk due to BMI. However, data from several studies suggest that the risk of prostate cancer due to BMI first lowers as BMI increases and then rises as BMI increases further. Nilson and coworkers [2] in their study of 22,248 Norwegian men found that the lowest risk of prostate cancer was associated with BMI values between 23.1 and 24.7. Nomura and coworkers [12] in a study of 8006 Japanese men from 1965 to 1968 found that the minimum risk of prostate cancer was for males whose BMI values were in the second quintile. Hsing and coworkers [18] in their study of 238 cases of newly diagnosed prostate cancer included BMI and history of BMI in their analysis. For current BMI values, the minimum risk of prostate cancer occurred in the third quartile of BMI. Historical evidence indicated that for BMI values in the first quartile, 20-29 year olds had the lowest risk of prostate cancer. However, for all other historical age ranges presented, the minimum risk of prostate cancer occurred in the second or third quartile.

It should be noted that in studies where the minimum risk of prostate cancer as related to BMI occurred in the 2nd or 3rd quartile, the investigators concluded that there was no relationship between BMI and risk of prostate cancer. Our experience with the NHIS data also produced this negative result before we modeled using a J-shaped curve. Given our finding, some of these earlier studies may merit further analysis.

Other studies [19, 20] that found no relation between BMI and the risk of prostate cancer reached this conclusion because there was no statistically significant difference between the mean BMI value of males that developed prostate

cancer and the mean BMI value of males that did not develop prostate cancer. Our experience with the NHIS data also indicated that there was no statistically significant difference between the mean BMI values of males that developed prostate cancer and males that did not develop prostate cancer. Correspondingly, these datasets may also warrant further analysis.

When we fitted the Cox proportional hazards model without assuming a J-shaped curve, we produced a BMI coefficient that was almost equal to zero. Therefore, if a J-shaped curve is not assumed, the data do not support a relationship between BMI and risk of prostate cancer. However, when we determined a change point value, two solid models (p-values ¡.02) were produced for the populations on each side of the change point. We acknowledge that many questions arise concerning the biological explanation as to why low BMI values may be producing higher risks of prostate cancer. In particular, given that the relationship persists when deaths occurring within two years of the interview are removed from the population. However, the assumption of a J-shaped curve was necessary to obtain meaningful models relating BMI to the risk of prostate cancer in these data.

In conclusion, our analyses do not show the data from the NHIS to support a relationship between BMI and risk of prostate cancer in black males. We found that these data do support a J-shaped risk curve to describe the relationship between BMI and risk of prostate cancer in white males. It may be that the increased risk of prostate cancer in white males with low BMI values is a result, rather than a cause, of prostate cancer. Or there may be other confounding factors responsible for this result. However, the inverse relationship between the risk of prostate cancer and low BMI persisted when deaths within two years of the interview were removed indicating that imminent death does not solely explain the J-shaped curve. There are other studies [18, 2, 12, 19, 20] with similar or shorter followup periods that found no relationship between low BMI values and risk of prostate cancer in any population. But some of these studies may have yielded results similar to ours had a j-shaped curve been tried. It may be worthwhile to re-examine some of these datasets, and future case control and cohort studies may wish to consider the J-shape curve in relating BMI to risk of prostate cancer to ensure that a true relationship between these factors is not overlooked.

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Number, Average BMI, Average Income, and Average Education by Race and Agegroup for Prostate Deaths, Other Deaths, and the Living

	Prostate Deaths				Other Deaths				Living			
	No.	BMI	Income	Educ	No.	BMI	Income	Educ	No.	BMI	Income	Educ
Blacks												
40 - 49	1	32.4	.	12	399	26.9	22811	11.3	6082	26.7	31748	12.2
50 - 59	20	28.5	22742	10.3	604	26.5	22724	10.1	4107	27.1	29842	11
60 - 69	62	26.6	19039	9.8	1003	25.9	17926	8.8	3037	26.7	22309	9.7
70 - 79	77	26.2	15511	7.5	847	25	14821	7.8	1378	26	16866	8.6
80 +	35	24.1	14716	6.8	438	24.1	12305	6.3	313	24.6	13323	6.8
Whites												
40 - 49	11	27.9	42136	13.4	1337	26.9	35086	12.5	44712	26.6	43223	13.7
50 - 59	24	26.5	44048	12.8	2631	26.6	33621	11.8	30503	26.8	42278	13
60 - 69	166	26.7	33686	11.8	5472	26	27213	11.4	24117	26.4	33235	12.3
70 - 79	287	25.1	24804	11.4	6722	25.1	22486	10.8	12302	25.6	25964	11.6
80 +	167	23.7	20676	10.1	3912	23.6	20736	10.1	2697	24.6	22359	10.8

Table 1

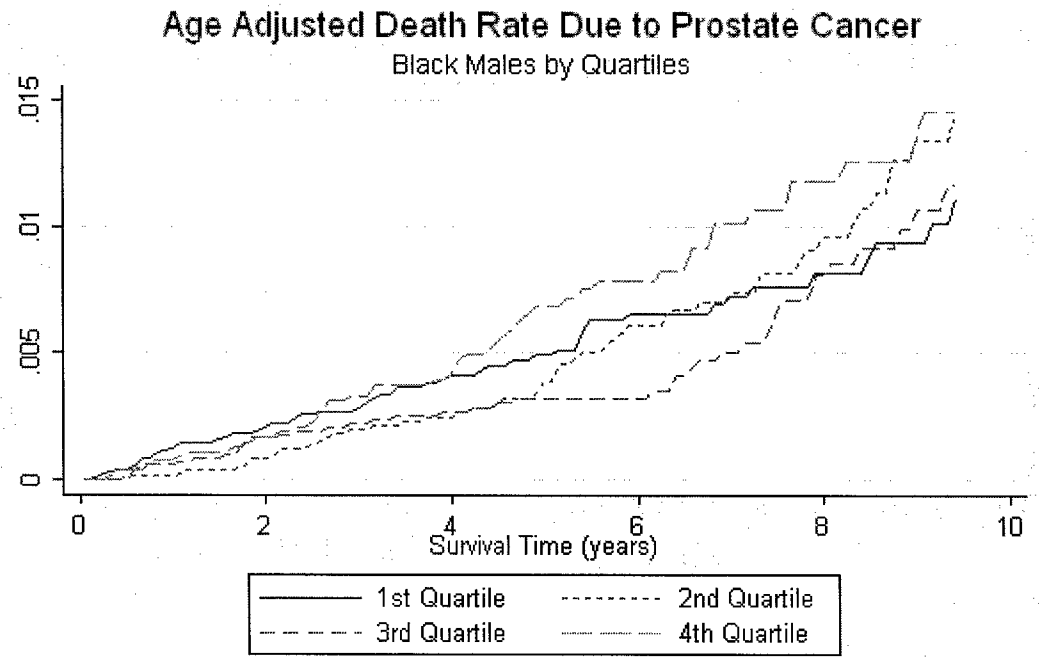

Figure 1

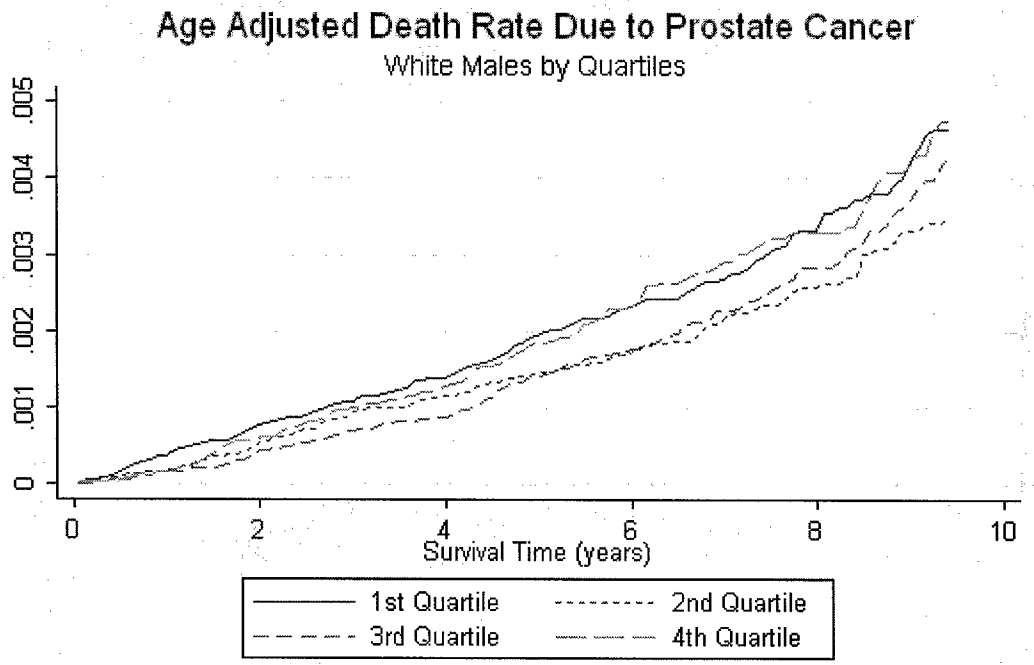
Age Adjusted Death Rate Due to Prostate Cancer
White Males by Quartiles
0
.001
.002
.003
.004
.005
0
2
4
6
8
10
Survival Time (years)
1st Quartile
2nd Quartile
3rd Quartile
4th Quartile

Figure 2

BMI Coefficients for Cox Regression Models using Age as a Covariate and Performed on 3 Distinct Populations

	All White Males over 40	White Males over 40 with BMI < 24.8	White Males over 40 with BMI => 24.8
BMI Coefficient	-0.003	-0.075	0.041
Standard Error	0.011	0.028	0.017
P-value	0.758	0.008	0.017
95% Conf. Interval	[-0.025, 0.018]	[-0.129, -0.020]	[0.007, 0.075]
P-value of Likelihood Ratio Test for BMI	0.757	0.009	0.022

Table 2

Overall Death Rate and Age Adjusted Death Rate For White Males by Quartiles of BMI

Quartile	Deaths	N	Rate	Age Adjusted Rate	SE(AAR)	95% Confidence Interval
1	7,855	34,875	0.225	0.184	0.00083	0.1822 - 0.1856
2	4,834	34,467	0.140	0.138	0.00074	0.1370 - 0.1399
3	4,156	31,793	0.131	0.135	0.00074	0.1338 - 0.1367
4	4,304	33,445	0.129	0.150	0.00080	0.1448 - 0.1512

Table 3

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ELSEVIER

Nutrition, Metabolism & Cardiovascular Diseases

Wide pulse pressure is an independent predictor of cardiovascular mortality in Puerto Rican men

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Summary *Background and aim:* Emerging evidence suggests that pulse pressure is an independent predictor of risk for cardiovascular mortality. New studies in diverse populations are needed to further establish the applicability of this finding. Thus, the purpose of this study is to examine the relationship between pulse pressure and cardiovascular mortality in a cohort of Puerto Rican men after 12 years of follow-up.

Methods and results: The Puerto Rico Heart Health Program is a study of coronary disease risk factors in men aged 35-79 years at baseline who had an initial examination during the years 1962–1965. It was attended by 9824 subjects representing 80% of the total age-specific male residents in 4 rural and 3 urban areas of Puerto Rico. Cardiovascular risk factors including systolic and diastolic blood pressures were monitored prospectively. This study includes 9106 men free of overt CHD at baseline who were stratified by quartiles of pulse pressure in mmHg: quartile 1, ≤ 38, quartile 2, 39–46; quartile 3, 47–56; and quartile 4, ≥ 57. The odds ratio of cardiovascular mortality was calculated using logistic regression analysis.

After adjusting for age, education, smoking status, hypercholesterolemic status, physical activity, diabetic status and mean arterial pressure, we found that those in

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the highest quartile of pulse pressure (pulse pressure > = 57) had significantly higher cardiovascular mortality than those in the lowest quartile (reference group) (OR = 1.38 95% CI = 1.01–1.88).
Conclusion: Our findings showed that a wide pulse pressure is independently associated with cardiovascular mortality in this group of Puerto Rican men.

Introduction

Studies regarding the importance of blood pressure as a determinant risk factor for the development of cardiovascular disease have been mainly focused on the study of the effect of systolic and diastolic blood pressures. More recently, added attention has been given to pulse pressure (defined as systolic minus diastolic blood pressure) as a possible independent predictor of risk for cardiovascular disease [1–5]. Average systolic blood pressure in the population increases progressively with age, while the increase in average diastolic blood pressure levels around the sixth decade (age 50–59) and starts to decline after 60 years of age [6,7]. The increase in pulse pressure with increasing age is a reflection of an important pathophysiologic phenomenon that includes an increase in stiffening of the large arteries and a decrease in arterial compliance [1–3,8–11]. This leads to an increase in pulse pressure with age, particularly after the age of 50 years. Age-related changes in pulse pressure have been reported in persons not receiving antihypertensive therapy and without coronary heart disease [12], while other studies have found isolated systolic hypertension to be a more important predictor of risk than pulse pressure [13].

There is a need to examine the effect of pulse pressure in a low CHD incidence population for which we have prospective data and well characterized cardiovascular risk factors throughout the follow-up period. Some of the unanswered questions about the independent effect of pulse pressure on cardiovascular mortality are its effect on minority populations and if these effects persist after controlling for mean arterial pressure and systolic blood pressure. Few prospective studies on minority populations have been carried out with careful attention to cardiovascular mortality as the outcome, using multiple examinations with standardized clinical assessments, and with small groups of untreated hypertensive participants at baseline to minimize the effect of blood pressure treatment.

Thus, the purpose of this paper is to study the independent effects of pulse pressure on cardiovascular mortality in a cohort of Puerto Rican men who took part in the Puerto Rico Heart Health Program.

Methods

Study design

The Puerto Rico Heart Health Program (PRHHP) is an epidemiological prospective study on risk factors for coronary heart disease that was initially attended by 9824 men. Briefly, information obtained included medical history, social history, smoking status, physical activity, dietary data, physical examination, body weight, blood pressure, skinfold measurements, vital capacity measurement, 12-lead ECG, urine sugar and albumin determinations, serum cholesterol, serum glyceride and lipoprotein electrophoresis. Follow-up examinations at 2.5, 5.25 and 8.25 years after the initial examination were conducted. A mortality surveillance at 12 years was completed [14–17].

Subjects

The population studied was a cohort of 9824 Puerto Rican men aged 35–79 years at time of initial contact. The cohort included both urban and rural subjects in a proportion of 2:1, in the population. A house to house census of the communities selected was conducted by the personnel that carried out the decennial census in order to identify the subjects. Appointments were given to the 12,167 subjects enumerated of which 9824 were initially examined from 1962 to 1965 representing 81% of all enumerated individuals in the 4 urban and 3 rural areas where the study was conducted. Persons with preexisting coronary heart disease at baseline were excluded from analysis and 9106 men constitute the sample for this study.

All the subjects had the systolic and diastolic blood pressure obtained by a physician with the subjects seated. The blood pressure was assessed twice following a standardized protocol and the second reading is being used to characterize systolic and diastolic blood pressures [18]. The

pulse pressure was assessed in millimeter of Hg in each subject by subtracting the baseline diastolic blood pressure from the baseline systolic blood pressure. We stratified our participants by quartiles of pulse pressure and calculated the odds ratio of cardiovascular mortality using multivariate logistic regression analysis.

Mortality and morbidity surveillance

A system was developed for morbidity and mortality surveillance of all subjects in order to detect all events of myocardial infarction, coronary insufficiency and cerebrovascular disease. Local hospitals were visited regularly. Any records of hospitalization or ECG findings acquired by this surveillance system were reviewed. Deaths among study subjects were ascertained by various means. The demographic registries of the areas under study were visited at regular intervals by a member of the study staff to copy death certificates of males of the corresponding age groups residing in the study area. An obituary search was made in all daily newspapers. At regular intervals, the office of Demography and Vital Statistics of the Department of Health of the Commonwealth of Puerto Rico provided a list of all men in the age groups who died anywhere in Puerto Rico. Each death certificate was checked against the listing of persons enumerated. Autopsies were continually monitored and in the case of participants on whom an autopsy was performed a copy of the autopsy protocol was obtained. At 12 years from initial examination, vital status was ascertained on all but 9 study participants who were designated as lost to follow-up. For this paper cardiovascular mortality will be the primary endpoint and refers to persons who died of sudden and non-sudden coronary heart disease, and cerebrovascular accidents.

Data analysis

The subjects were grouped into quartiles by levels of pulse pressure obtained at baseline. Multiple variables (age as a continuous variable; smoking categories: current, previous or never smoker; educational attainment: no formal education, 1–4 years, 5–8 years, high school, college; BMI categories: underweight, normal weight, overweight and obesity; quartiles of physical activity, diabetes status; high blood cholesterol status: <200 mg/dl, 200–239 mg/dl and 240+ mg/dl, and mean arterial pressure (defined as 2/3 DBP + 1/3 SBP) were included in the model and kept if they were statistically significant at the $P < 0.05$.

All statistical analyses were performed using the Statistical Analysis Software (SAS). Odds ratio of cardiovascular mortality was established using logistic regression analysis. Adjustments for mean arterial pressure (MAP) were done using the standardized form of mean arterial pressure (individual MAP − group mean MAP/group SD). Multiple logistic regression analysis was used to assess the effect of pulse pressure on cardiovascular mortality after 12 years of follow-up.

Results

Table 1 provides a description of baseline characteristics and cardiovascular risk factors of the study participants. Hypertension status was characterized as having systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg, currently taking antihypertensive medication, or normotensives (those having blood pressures below 140/90 mmHg).

Table 2 provides a description of blood pressures (means systolic blood pressures, diastolic blood pressures, and pulse pressures) of participants according to quartiles of pulse pressure. Although somewhat older (57 years), the average BMI (k/m^2), and percent of participants with high blood cholesterol (> = 240 mg/dl) and who were current smokers in quartile 4 were not substantially different than those in lower quartiles. The average systolic and diastolic blood pressure increased progressively from the first pulse pressure quartile to the fourth quartile.

Fig. 1 shows the unadjusted survival curve according to quartiles of pulse pressure levels. Decrease survival rates at the end of the follow-up period are observed among those in quartile 4 compared with those in quartiles 1–3. Table 4 illustrates the risk of cardiovascular mortality using 16 mutually exclusive groups of systolic and diastolic blood pressure (<120, 120–139, 140–159 and > = 160 mmHg by <70, 70–79, 80–89, and > = 90 mmHg). In general, increase in CVD mortality risk is observed with increasing levels of systolic (>140 mmHg) and diastolic blood pressure (>80 mmHg) levels when compared to the reference group SBP < 120 × DBP < 70 mmHg, with few exceptions (SBP = 140–159 mmHg × DBP < 70 mmHg; and SBP > = 160 mmHg × DBP < 70 mmHg).

Table 3 shows crude mortality and multivariate odds ratio of cardiovascular mortality according to

Table 1 Baseline characteristics of study participants

	N	%
Age groups (years)		
35–44	337	4
45–54	4665	51
55–64	3514	39
65+	590	6
Education		
No formal school	913	10
1–4 years	3201	35
5–8 years	2605	29
9–12 years	1625	18
12+ years	744	8
Rural/urban		
Rural	2778	31
Urban	6328	69
BMI category		
<18.5	291	3
18.5–24.9	4311	47
25–29.9	3407	37
30+	1097	12
Blood cholesterol (mg/dl)		
<200	1446	16
200–239	3011	33
240+	4649	51
Smoking status		
Never smokers	3113	34
Previous smokers	2017	22
Current smokers	3968	44
Hypertension status		
Untreated hypertensives	2655	29
Treated hypertensives	735	8
Normotensives	5716	63
Diabetes		
Yes	468	5
No	8537	94
Uncertain	101	1

Puerto Rico Heart Health Program. Column percentages may not add to 100 due to rounding.

quartiles of pulse pressure. The cardiovascular disease mortality at 12 years was higher in the subjects with pulse pressure in the fourth quartile than among those in quartiles 1 and 2. The risk of cardiovascular mortality was significantly increased in persons with a wide pulse pressure (quartile 4) even after adjusting for age, mean arterial pressure, education, smoking, high blood cholesterol, physical activity and diabetes status. We also calculated the odds ratio for cardiovascular mortality for 1 standard deviation (SD) differences in mean arterial pressure and pulse pressure as independent predictor of risk. We found the adjusted odds ratio for both mean arterial pressure (OR = 1.6, $P < 0.01$) and pulse pressure (OR = 1.2, $P < 0.01$) to be significantly related to cardiovascular mortality. No statistically significant interaction between mean arterial pressure and pulse pressure were observed.

Comments

We have presented the association between pulse pressure and cardiovascular mortality at 12 years of follow-up in a cohort of 9106 men in 4 rural and 3 urban areas in the Northeast region of Puerto Rico. Puerto Rican men with a pulse pressure greater than 57 (quartile 4) had a decreased survival rate compared to those with pulse pressure in quartile 1–3 (pulse pressure < 57) (see Fig. 1). The increase in cardiovascular mortality observed among Puerto Rican men in quartile 4 was sustained after controlling for other established risk factors for cardiovascular disease. A unique consideration of this cohort is that incidence and mortality from cardiovascular disease in this Hispanic population was lower than estimates in the US. Thus, pulse pressure is an independent predictor of cardiovascular mortality even among low incidence populations.

High pulse pressure is an independent predictor of cardiovascular mortality in both hypertensive and those with a normal blood pressure as reported by others [19–28]. However, other investigators found no association between pulse pressure and cardiovascular mortality [13,29]. To

Table 2 Description of participants by quartiles of pulse pressure (mean + SD)

Quartiles (range)	N	Age (years)	Current smokers (%)	High blood cholesterol (%)[a]	BMI	Systolic (mmHg)	Diastolic (mmHg)	Mean arterial pressure[b]	Pulse pressure
Quartile 1 (<38)	2408	52 (6.1)	45	14	24 (3.9)	111 (10.5)	79 (9.4)	89 (9.5)	32 (4.7)
Quartile 2 (39–46)	2460	53 (6.3)	45	15	24 (3.8)	122 (10.3)	80 (10.0)	94 (10.1)	43 (2.3)
Quartile 3 (47–56)	2115	54 (6.4)	43	17	25 (4.1)	134 (11.4)	82 (11.0)	99 (11.1)	51 (2.6)
Quartile 4 (> = 57)	2123	57 (6.4)	41	17	26 (4.8)	159 (21.1)	88 (14.3)	111 (15.7)	70 (13.2)

[a] High blood cholesterol = greater than or equal to 240 mg/dl.
[b] Mean arterial pressure = 2/3 DBP + 1/3 SBP.

Table 3 Crude and multivariate odds ratio of multivariate logistic regression of cardiovascular disease mortality according to quartiles of pulse pressure

Quartile (range)	CVD deaths	Crude	Model 1	Model 2	Model 3
Quartile 1 (<38)	91	Reference	Reference	Reference	Reference
Quartile 2 (39–46)	94	1.01 (0.75–1.36)	0.95 (0.71–1.28)	0.80 (0.59–1.08)	0.99 (0.74–1.34)
Quartile 3 (47–56)	125	1.60 (1.21–2.11)	1.39 (1.05–1.83)	0.92 (0.68–1.24)	1.39 (1.04–1.85)
Quartile 4 (> = 57)	340	4.86 (3.82–6.17)	3.56 (2.78–4.56)	1.38 (1.01–1.88)	3.33 (2.59–4.39)

Model 1: Adjusted for age.
Model 2: Adjusted for age (continuous), education, smoking status, high blood cholesterol status, diabetes status, physical activity, and mean arterial pressure.
Model 3: Adjusted for age (continuous), education, smoking status, high blood cholesterol status, diabetes status, physical activity, and residual of mean arterial pressure.

our knowledge, no study has examined the effect of pulse pressure in this exclusive group of minority population and using a cohort with low risk for cardiovascular mortality.

In 1960s the Puerto Rico Heart Health Program was designed to examine the relationship of CHD risk factors in a low CHD incidence population. Currently, age-adjusted rates of heart disease in Puerto Rico continues to be lower (205/100,000) than those observed in mainland of US (268/100,000) [30] and hypertension rates are also lower than those of non-Hispanic whites in the US [31]. Thus, our findings provide new information on the relationship of pulse pressure with cardiovascular mortality in a well characterized cohort of Hispanic men. Additionally, the cohort had few treated hypertensives (<8%) minimizing the influence of medication status on the final outcome. Another important aspect of our analysis is the inclusion of mean arterial pressure in the overall analysis to further characterize the relevant importance of pulse pressure in cardiovascular mortality. Overall we found that even after adjusting for mean arterial pressure, men in the higher quartile (> = 57 mmHg) were at significantly higher risk for cardiovascular mortality than those in quartile 1 (<38 mmHg).

Blacher et al. in a meta-analysis of the European Working Party on High Blood Pressure in the Elderly Trial ($n = 840$), the Systolic Hypertension in Europe Trial ($n = 4695$), and the Systolic Hypertension in China Trial ($n = 2394$) report that in older hypertensive patients pulse pressure, and not mean arterial pressure was the major determinant of cardiovascular risk [25]. We found both mean arterial blood pressure and pulse pressure to be independently associated with cardiovascular mortality. This may be due to the differences in population under study, baseline treatment levels or age of participants.

To more clearly understand the role of systolic and diastolic blood pressure, and pulse pressure on CVD related mortality, Domanski et al. used data on 342,815 men from the Multiple Risk Factor Intervention Trial (MRFIT). Participants were grouped into 2 age groups (35–44 years old, and 45–57 years old) and CVD mortality rates were studied according to multiple categories of systolic and diastolic blood pressure using the JNC VII categories [32]. In both groups, SBP and DBP were

Table 4 Odds Ratio of cardiovascular mortality according to levels of systolic and diastolic blood pressure

Diastolic BP (mmHg)	Systolic BP			
	<120 mmHg	120–139 mmHg	140–159 mmHg	160+ mmHg
<70	Reference (1.0)	1.35 (0.53–3.44)	3.61 (0.82–15.94)	6.70 (0.54–82.82)
	19/757	6/133	3/20	2/6
70–79	1.25 (0.71–2.18)	1.71 (0.99–2.96)	3.77 (1.94–7.31)	10.64 (3.93–28.84)
	39/1337	46/970	21/167	10/29
80–89	2.04 (1.14–3.66)	1.76 (1.06–2.91)	2.54 (1.46–4.43)	8.02 (4.21–15.28)
	31/669	87/2008	45/601	29/113
90+	–	2.51 (1.38–4.56)	3.24 (1.92–5.46)	9.97 (6.12–16.26)
	0/18	30/508	71/872	209/882

Adjusted for age, diabetes, education, high blood cholesterol, physical activity and smoking status.
Numbers below odds ratio represent CVD events and total number of persons in systolic/diastolic blood pressure group.

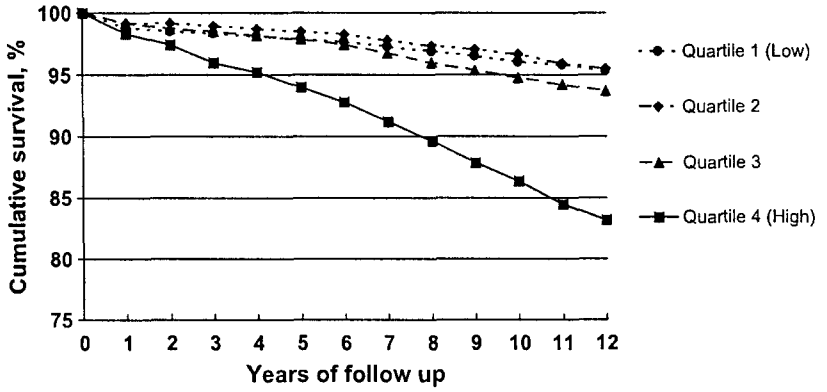

Figure 1 Unadjusted survival curve for cardiovascular disease by quartiles of pulse pressure, 12 years follow-up.

more strongly associated with cardiovascular disease mortality than pulse pressure. With a relatively smaller sample size we calculated the CVD mortality risk using various categories of systolic (<120, 120–139, 140–159 and 160+ mmHg) and diastolic blood pressure (<70, 70–79, 80–89, and 90 mmHg) as suggested by others [12,33]. We found an increased risk of CVD mortality with increasing levels of systolic and diastolic blood pressure.

In a longitudinal study conducted by the Veterans Administration at the Boston Outpatient Clinic Lee et al. found that in the elderly male, pulse pressure, may be a more accurate predictor of cardiovascular death than either systolic blood pressure or diastolic blood pressure alone [27]. Other investigators [13,29] have found that the increased risk of CVD mortality is more strongly associated with systolic blood pressure than with pulse pressure. Thus, not all studies have found pulse pressure to be an independent risk factor, however variations in systolic and diastolic blood pressure were not systematically taken into consideration. In our multivariate logistic regression analysis we included mean arterial pressure to adjust for the relative contributions of systolic and diastolic blood pressure.

A critical aspect of the statistical analysis is that pulse pressure is derived from systolic and diastolic blood pressure, and therefore are highly correlated [34]. Moreover, the definition of mean arterial pressure includes pulse pressure. Because of collinearity among blood pressure components there is considerable overlap between pulse pressure and mean arterial pressure, systolic blood pressure and diastolic blood pressure in predicting cardiovascular mortality. At any given pulse pressure, the collinearity with SBP is maximized when DBP is high and minimized when DBP is normal or low [12]. Millar et al. found that the correlation of pulse pressure with SBP was much stronger than with diastolic blood pressure [24]. Thus, it is important to take into account the effects of systolic and diastolic blood pressure when examining the relationship of pulse pressure and CVD related mortality, since the prevalence of hypertension in the geriatric population exceeds 50% and includes isolated systolic hypertension with large pulse pressure levels in approximately two thirds of cases [35]. This is of clinical and public health importance since the most common type of untreated hypertension among adults and Hispanics is the isolated systolic hypertension [6,31,36–38].

An analogous strategy used in nutritional epidemiology to study highly correlated variables such as saturated fat, total fat, and total energy intake, is to use the residual method of adjustment [39]. Because systolic blood pressure and mean arterial pressure were highly correlated with pulse pressure ($R = 0.62$, $P < 0.01$ and $R = 0.86$, $P < 0.001$, respectively) we calculated the odds ratio using the residual method of adjustment. Briefly, pulse pressure adjusted for mean arterial pressure was calculated as the residuals from a regression model with mean arterial pressure as the independent variable and pulse pressure as the dependent variable. The resulting residuals provide a measure of pulse pressure uncorrelated with mean arterial pressure, and these residuals were then used in subsequent multivariate analyses. We found significantly higher CVD mortality among those in quartile 4 of pulse pressure than among those in the reference group (quartile 1) using the residuals of mean arterial pressure and systolic blood pressure levels. Further adjustment for age and other covariates did not change these results (data not shown).

Various studies hereby quoted have shown that there is a progressive increase of pulse pressure with aging. The linear rise in systolic blood pressure has been reported from age 30 through 84 years. After the age of 60 years there is the

decline in diastolic blood pressure. The decline in diastolic pressure is mainly due to age-related stiffening of the aorta, which is mostly an effect of progression of atherosclerotic lesions. The increase of systolic blood pressure tends to increase the left ventricular pulsatile work which requires a greater coronary blood flow. The decline in diastolic pressure reduces the pressure on which coronary flow is dependent increasing the vulnerability of the heart to ischemia. In view of this, it seems logical to postulate that pulse pressure itself could be used as a major predictor of cardiac risk. Our findings, as well as of others quoted in this article, is that pulse pressure is a predictor of cardiovascular death even after adjusting for mean arterial pressure [13,19–28,40,41].

We conclude that wide pulse pressure, defined as, quartile 4 of pulse pressure ($> = 57$ mmHg), was an independent predictor of cardiovascular mortality after adjustment for mean arterial pressure and other covariates. This highlights the effect of wide pulse pressure in a different cohort composed of Puerto Rican men with low coronary heart disease incidence which has clinical and public health significance, since Hispanics have one of the lowest rates of awareness, treatment and control of hypertension [6,31]. This cohort of men, also, had few hypertensives being treated at baseline (8%), which differentiate our results from other findings reported in the literature.

The finding that high pulse pressure is a predictor of cardiovascular death in this population points to the possible value of using the pulse pressure measurement in the clinical evaluation of individuals risk and as a guide for the institution of preventive measures in those elderly individuals with a high pulse pressure level who may benefit from treatment to improve arterial compliance. Pulse pressure may also serve as a possible aid in the stratification of hypertension for management purpose. Widened pulse pressure may also be indicative of atherosclerosis, which may explain why the odds ratio for quartile #4 is not as robust as in other studies. More recently, data from the National Health and Nutrition Examination Survey found that older hypertensive subjects who used diuretics alone or in combination with beta-blockers had lower mean pulse pressure than those using beta-blockers [42]. More research, however, is needed to examine the possible benefits of therapeutic approaches specifically designed to address the vascular pathology present with high pulse pressure.

Trials may be indicated to explore if reversal of coronary risk can be obtained with antihypertensive drugs that decrease pulse pressure or that might have a relative specific effect on systolic blood pressure by decreasing arterial stiffness.

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Association of Cigarette Smoking, Alcohol Consumption, and Physical Activity With Lower Urinary Tract Symptoms in Older US Men – Findings from the Third National Health and Nutrition Examination Survey (NHANES III)

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Abstract

Objectives: To examine the association of cigarette smoking, alcohol consumption, and physical activity with lower urinary tract symptoms (LUTS).

Design. Cross-sectional study.

Setting. Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study representative of the US population.

Participants. 2881 male participants who were 60 years and older.

Measurement. During an interview, lower urinary tract symptoms, smoking history, alcohol consumption, and physical activity were assessed. The case group consisted of men with at least three of the four following symptoms: nocturia, hesitancy, weak stream, and incomplete emptying. Men who had had non-cancer prostate surgery were not included in the case group. Controls were men without symptoms and surgery. We adjusted for age and race in logistic regressions models and used sampling weights to account for selection probability.

Results: Current cigarette smokers did not have a higher odds of LUTS compared to never smokers. However, former heavy smokers (50+ pack-years) had an elevated odds of LUTS compared to never smokers (OR = 2.01; 95% CI 1.04-3.89). Men who drank alcohol daily had a decreased odds of LUTS compared to non-drinkers (OR = 0.59; 95% CI 0.37-0.95; p-trend 0.07). All levels of moderate and vigorous activity were statistically significantly inversely associated with LUTS (p-trend = 0.06), whereas men who did not report any physical activity had an increased odds of LUTS (OR = 2.06; 95% CI 1.26-3.39).

Conclusions: Moderate alcohol consumption and physical activity may be protective of LUTS. Current cigarette smoking was not consistently associated with the condition. The possible association in former smokers warrants further investigations.

Key words. NHANES III, LUTS, smoking, physical activity, alcohol consumption

Introduction

Lower urinary tract symptoms (LUTS) are a common bothersome condition in older men. Although benign prostatic hyperplasia is thought to be one cause of these symptoms not all men with symptoms have an enlarged prostate.[Thorpe, 2003 #327] Changes in the tone of prostate and bladder smooth muscle may also contribute to these symptoms. Despite the high prevalence of LUTS not much is known about their etiology. Age is the only well-established risk factor, but it has been hypothesized that common lifestyle factors such as smoking, consumption of alcohol, or physical inactivity might contribute to the symptomology.

While physical activity generally has been found to be inversely associated with the prevalence of LUTS,[Platz, 1998 #46][Prezioso, 2001 #201] and BPH[Meigs, 2001 #151][Gann, 1995 #121] the associations of cigarette smoking and alcohol consumption with LUTS and BPH are more controversial. Most studies found either no[Klein, 1999 #298][Roberts, 1994 #300][Roberts, 1997 #299][Haidinger, 2000 #144][Prezioso, 2001 #201][Lee, 1997 #120] or a positive[Joseph, 2003 #191][Koskimaki, 1998 #285][Platz, 1999 #43] association between cigarette smoking and LUTS. Fewer studies have evaluated the association of alcohol intake with LUTS; two studies observed an inverse association[Platz, 1999 #43][Klein, 1999 #298], whereas others saw positive associations.[Haidinger, 2000 #144][Prezioso, 2001 #201][Joseph, 2003 #191]

NHANES III is a large American cross-sectional study that was conducted between 1988 and 1994. Using the data collected in NHANES III, we evaluated the association of cigarette smoking, alcohol consumption, and physical activity with LUTS in a multi-ethnic group of older men representative of the US.

Material and Methods

Study population: NHANES III is a nationally representative cross-sectional study of the non-institutionalized civilian US population conducted between 1988 and 1994[National Center for Health Statistics, 1994 #150]. A multistage probability sampling design was used with oversampling of non-Hispanic blacks, Mexican-Americans, and older participants. Subjects participated in an interview conducted at home and underwent an extensive physical examination. In our analysis, we included 3117 men who were 60 years and older at participation. Of these, we excluded those men with a mobility impairment (n = 103) or who were not self-respondents (n = 133). We further excluded 84 men who reported during the interview having had a prostate cancer diagnosis at some point prior to the interview. The remaining 2797 men were included in the analysis.

Outcome assessment: During the interview, all men who were 60 years and older were asked for the following symptoms, which are part of the American Urological Association symptom index[Barry, 1992 #133]: a) How many times per night do you usually get up to urinate (pass water)? ("nocturia"), b) when you urinate (pass water), do you usually feel like you have not completely emptied your bladder? ("incomplete emptying"), c) do you usually have trouble starting to urinate (pass water)? ("hesitancy"), and d) has the force of your urinary stream of water decreased over the years? ("weak stream"). In the present analysis, men were considered as having LUTS if they reported at least three of the four symptoms. Nocturia was included as a symptom when men had to get up at least twice per night. Men were also asked if they had ever had surgery for their prostate not related to cancer ("non-cancer prostate surgery"). Those men who reported non-cancer prostate surgery were excluded from the case group because the removal of the hyperplastic tissue may have reduced or eliminated symptoms. The controls were men who did not report any of the four

symptoms and had never had non-cancer prostate surgery. Men with only one or two symptoms were excluded from the analysis to increase the specificity of the LUTS definition.

Exposure assessment: Smoking history was assessed during the interview and men were classified according to their current smoking habit into current (1-34, or ≥ 35 cigarettes per day), former, or never smokers. We also calculated pack-years of smoking from smoking history. A pack-year was defined as 20 cigarettes per day for one year. The consumption frequency of alcoholic beverages (beer, wine, liquor) during the past month was assessed using a food frequency questionnaire during the interview. This method captures long-term habits of alcohol consumption. We categorized men into those who did not consume any of these three alcoholic beverages, those who drank up to once per week, more than once per week but less than once per day, and those who drank alcohol once a day or more. During the physical examination at the Mobile Examination Center a 24-hour dietary recall was administered, which assessed the amount of alcohol consumed during the previous day. From these data, the daily intake of alcohol in grams was calculated. We grouped men as having a daily intake of 0 g/d, 1-15 g/d, 16-37 g/d, or 38 g or more per day. Further, type and frequency of leisure time physical activity were obtained during the interview. Physical activities were coded and classified by rate of energy expenditure (i.e. by intensity) according to a standardized coding scheme developed by Ainsworth et al.[Ainsworth, 1993 #353]. Men were grouped by their weekly frequency of moderate and vigorous activity. Moderate activity included walking, jogging or running, biking, swimming, aerobics, dancing, calisthetics, gardening, lifting weights, and other physical activities if the metabolic equivalent of the activity compared to at rest (METs) were > 2.4 for men aged 60-64, > 1.9 for men aged 65-79, or > 1.25 for men aged > 79. Vigorous activity was defined as walking (for men aged > 79), jogging or running, biking (for men aged > 64), swimming, aerobics, dancing (for men

aged > 64), calisthetics (for men aged > 64), gardening (for men aged > 64), lifting weights (for men aged > 79), and other physical activity if METs were > 5.9 for men aged 60-64, > 4.7 for men aged 65-79, or > 2.9 for men aged > 79[U.S. Department of Health and Human Services, 1996 #346]. Waist circumference of the participants was measured during the physical examination. Men were considered to have a history of hypertension if they currently used medication to treat hypertension or if they were told by their doctor on two occasions that they had hypertension/high blood pressure.

Statistical analysis: Statistical analyses were performed using SAS v8.1 (SAS Institute, Cary, NC) and SUDAAN[Shah, 1995 #124] software. We used sample weights that took into account several features of the NHANES III survey: the specific probabilities of selection for the individual domains that were over-sampled as well as non-response and differences between the sample and the total U.S. population[National Center for Health Statistics, 1994 #150].

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) of LUTS for cigarette smoking, alcohol consumption, and physical activity. In the logistic regression models, we adjusted for age (5-year categories) and race (non-Hispanic black, non-Hispanic white, Mexican-American, other). We further included in the models waist circumference (continuous variable) as a possible confounder and mutually adjusted cigarette smoking, alcohol consumption, and physical activity. Trend tests for alcohol consumption and physical activity were performed by assigning to each man the median value for the exposure category into which he fell and modeling this term as a continuous variable, the coefficient for which was evaluated by the Wald test.

Results

Of the 2797 men in the analysis, 28.8% did not have any of the lower urinary tract symptoms and had never had non-cancer prostate surgery (controls), 46.7% reported one or two symptoms, and 10.3% reported three or four symptoms (cases). Men with LUTS were older than men in the control group and had fewer years of education (Table 1). These men also drank less alcohol, but smoking patterns and weekly frequency of physical activity did not differ.

Men who currently smoked up to 35 cigarettes per day did not have an elevated odds of LUTS, but we observed a non-statistically significant elevated odds of LUTS in men who smoked 35 or more cigarettes per day (Table 2). However, this association was strongly attenuated after adjusting for waist circumference, the frequency of alcohol consumption, and the frequency of moderate and vigorous activity. Of these factors, waist circumference caused the strongest attenuation of the odds ratio for heavy smoking. Former smokers had a slightly, but not statistically significant, higher odds of LUTS compared to never smokers. Men who had ever smoked 50 or more pack-years had a higher odds of LUTS than never smokers. This association was limited to formers smokers; there was no association among current smokers who had smoked 50 or more pack-years. Further adjustment for waist circumference, but not for hypertension, attenuated the association of pack-years with LUTS in both ever and former smokers.

We observed an inverse association between the frequency of alcohol consumption and LUTS in this group of older men (Table 3). Compared to non-drinkers, men who drank alcohol daily had a significantly lower odds of LUTS. This association was not substantially altered after adjusting for waist circumference, physical activity, and cigarette smoking, or after adjusting for hypertension. Using a second approach to assess alcohol consumption by

24-hour dietary recall, men with a daily alcohol intake of 38 g/day or more had a lower odds of LUTS compared to men with no alcohol intake (OR = 0.41; 95% CI 0.14-1.20; p-trend = 0.08).

Men who did not report any leisure time physical activity had a significantly higher odds of LUTS than men who reported some physical activity (OR = 2.09; 95% CI 1.25-3.48) and adjusting for smoking, alcohol intake, and waist circumference did not change this association. All levels of moderate or vigorous physical activity were also associated with a significantly reduced odds of LUTS compared to men who did not report moderate or physical activity (Table 4). These results did not change after further adjusting for history of hypertension or for the presence of the metabolic syndrome (data not shown). However, vigorous physical activity alone was not consistently inversely associated with LUTS. The most frequently reported activity was walking. Fewer men with LUTS than men without LUTS reported walking (33.2% vs. 50.8%, p-value = 0.003). Men who reported walking had a lower odds of LUTS compared to men who did not, although the odds did not decrease monotonically (Fig. 1). Adjusting for total frequency of moderate and vigorous physical activity as well as waist circumference, smoking, and alcohol drinking did not change the association for walking.

Discussion

In this group of older US men, alcohol consumption and moderate and vigorous physical activity were both inversely associated with LUTS. Men who walked regularly were less likely to have LUTS than men who did not. We did not observe an association between current cigarette smoking and LUTS, but could not rule out the former heavy smokers were more likely to experience LUTS.

Several studies have examined the association between cigarette smoking and LUTS with inconsistent results. Most studies have not observed a statistically significant association between cigarette smoking and LUTS,[Klein, 1999 #298][Roberts, 1994 #300][Roberts, 1997 #299][Haidinger, 2000 #301][Prezioso, 2001 #201][Lee, 1997 #120] whereas three studies have observed a statistically significantly positive association.[Koskimaki, 1998 #285] [Joseph, 2003 #191] In an analysis of the Health Professionals Follow-up Study,[Platz, 1999 #43] heavy smokers had a significantly higher risk of LUTS than never smokers, whereas moderate smokers did not have an elevated risk. Similarly, in NHANES III, we did not observe an association for current cigarette smoking but noted a suggestion of a higher occurrence of LUTS in heavier current, lifetime, and former smokers.

There may be several explanations for LUTS possibly being more common in long-term heavy smokers. Smooth muscle is one of the dominant cellular components of the prostate and its tension is mediated by the alpha-1-adrenoreceptor. Thus, higher systemic sympathetic nervous activity may increase the tonus of prostate smooth muscle. Additionally, heightened sympathetic nervous system activity might affect the tonus of bladder smooth muscle.[Michel, 2000 #229] Nicotine increases sympathetic nervous system activity[Narkiewicz, 1998 #309] and might contribute to LUTS via an increase in the tone of the prostate and bladder smooth muscle. Alternatively, smoking influences the metabolism

of sex steroid hormones. Smoking is associated with higher concentrations of testosterone in some,[Svartberg, 2003 #310][Allen, 2002 #137][English, 2001 #325] although not all studies.[Hsieh, 1998 #326] A higher testosterone concentration might be associated with higher intraprostatic dihydrotestosterone levels. Dihydrotestosterone is thought to be important in the development of benign prostatic hyperplasia and LUTS[Carson, 2003 #313].

We observed a slightly elevated odds of LUTS in former smokers and these men also had a higher odds of LUTS when they smoked 50 or more pack-years over lifetime. Platz et al.[Platz, 1999 #43] also observed a higher risk of LUTS in former smokers. The reasons for an elevated odds of LUTS in former smokers are not clear. We observed a higher waist circumference, which might be associated with insulin resistance, in former than in current smokers but adjusting for waist circumference did not attenuate the association of former smoking with LUTS. Whether possible effects of sex steroid hormone metabolism on the prostate caused by smoking in the past influences current symptoms is not known. Also, we cannot rule out chance as an explanation for this finding.

Men who frequently consumed alcohol were less likely to have LUTS compared to men who did not drink alcoholic beverages. We also noted a lower odds of LUTS with increasing daily alcohol intake when using a second dietary assessment tool that captured intake the day before the interview. These results support the findings of two others studies that observed inverse associations between alcohol consumption and LUTS,[Platz, 1999 #43][Klein, 1999 #298] whereas Haidinger et al.[Haidinger, 2000 #144] and Prezioso et al.[Prezioso, 2001 #201] observed positive associations between alcohol consumption and LUTS or clinically diagnosed BPH. Platz et al.[Platz, 1999 #43] saw a decreased odds in moderate drinkers, but this protective effect was attenuated in men who consumed more than 50 g alcohol per day

(about 3.5 or more drinks per day). This pattern was also seen in another US cohort study, in which African-American men with an intake of more than 72 g/day (about 5 or more drinks per day) had a significantly higher odds of LUTS than non-drinkers, whereas they did not observe an association in moderate consumers.[Joseph, 2003 #191] In NHANES III, few men reported an alcohol intake of 50 g or more per day and we cannot determine whether we would also observe an attenuation of the inverse association of alcohol with LUTS in groups with a higher consumption. Further, we cannot rule out that the observed inverse association between the frequency of alcohol consumption and LUTS is due to avoidance of fluids, especially of alcoholic beverages that have a diuretic effect, by men with LUTS since we observed a non-statistically significantly reduced odds of LUTS in men who drink caffeinated beverages at least four times a week (data not shown).

In NHANES III, men who were physically active in their leisure time were less likely to have LUTS. All levels of moderate and vigorous activity were inversely associated with LUTS, but the association for vigorous activity was not consistently decreasing. Few studies have examined the association between physical activity and the odds of LUTS.[Platz, 1998 #46][Prezioso, 2001 #201] Both groups observed inverse associations between frequency of physical activity and LUTS. Lacey et al.[Lacey, 2001 #203] observed a slightly inverse association between the intensity of occupational physical activity, but not recreational activity, and the risk of BPH in a study in Chinese men.

Physical activity is associated with improved insulin sensitivity.[Henriksen, 2002 #303][Borghouts, 2000 #324][Goodpaster, 2003 #360] We previously found statistically significant positive associations of glycosylated hemoglobin, a long-term marker of glucose and insulin metabolism, and the metabolic syndrome with LUTS in this group of men (Rohrmann et al., submitted). Alternatively, reductions in the odds of LUTS due to physical

activity might be caused by changes of sympathetic nervous system activity. Brown et al.[Brown, 2002 #304] hypothesized that aerobic exercise training may elicit adaptations in the adrenergic system, because the sympathetic nervous system is activated through each bout of exercise, and repeated activation of the sympathetic nervous system could result in an reduction of the resting sympathetic nervous system activity. In contrast to Platz et al. [Platz, 1998 #46] we did not observe a consistently inverse association between vigorous physical activity and LUTS. Only men who reported vigorous activity up to twice a week had a statistically significantly reduced odds of LUTS, but the association was weaker in men who were more vigorously active. However, in this general population, few men reported participating in vigorous physical activity more than twice a week.

In addition to an inverse association between total moderate and vigorous activity, we also observed that men who walked, the most often reported type of physical activity in this group of older men, were less likely to have LUTS. This association has previously been noted in the Health Professionals Follow-up Study.[Platz, 1998 #46] A small case-control study in Japan[Iwane, 2000 #361] observed that walking 10,000 steps or more per day for 12 weeks was inversely associated with sympathetic nervous activity and blood pressure in hypertensive men compared to sedentary men. Therefore, men who walk regularly might be less likely to experience lower urinary tract symptoms due to lower tone of the prostate and bladder smooth muscle and due to lower blood pressure, which has previously been shown to be positively associated with LUTS.[Hammarsten, 1998 #117][Joseph, 2003 #191](Rohrmann et al., submitted)

Several aspects of the study design merit further discussion. First, NHANES III is a cross-sectional study representative of the US population of older men, thus, aiding in the broad generalizability of these results. Also, the elderly were over-sampled allowing for more

stable estimates in our analysis in older men. Second, the questions on LUTS in NHANES III covered four of the seven questions of the American Urological Association symptom index which additionally comprises frequency, intermittence, and urgency, which together were found to discriminate between men with and without benign prostate hyperplasia in a clinical setting.[Barry, 1992 #133] To increase the specificity of our analysis, we included only men with three or four symptoms in the case group. We did not include men with only one or two symptoms in the control group or in the case group because individually these symptoms are not specific for LUTS. Third, we cannot completely rule out that some men in the control group did not report lower urinary tract symptoms due to intake of medications to treat their symptoms. However, this is unlikely because NHANES III was conducted between 1988 and 1994 and medication for the treatment of BPH symptoms was not approved until 1992 (Finasteride)[Nightingale, 1992 #308][Food and Drug Administration, #307] and 1993 (terazosin).[, 1994 #306] Finally, smoking, alcohol consumption, and physical activity were assessed concurrently with LUTS. Therefore, the results reflect associations and are not necessarily causal.

In conclusion, physical activity, even moderate activities like walking, may be beneficial for LUTS. Additionally, moderate alcohol consumption might be associated with a reduction in the occurrence of LUTS, whereas heavy cigarette smoking in the past may increase the occurrence of LUTS in older men. Intervention studies are needed to determine whether the frequency of LUTS can be modulated by changes in these lifestyle factors.

TABLE 1. Age-Adjusted Baseline Characteristics* of Male Study Participants, Age 60 and Older, NHANES III 1988-1994

	Controls (no LUTS, no surgery)	Cases (3 or 4 symptoms, no surgery)	p value
Unweighted sample size	715	320	
Percent of total sample	28.8	10.3	
Age, mean (SE†)	67.6 (0.3)	71.0 (0.6)	< 0.001‡
Current waist circumference, mean (SE) [cm]	100.4 (0.66)	101.2 (0.65)	0.46‡
Years of education, mean (SE)	11.3 (0.2)	10.4 (0.4)	0.03‡
Smoking habits			
Never smokers [%]	28.7	23.6	0.21§
Former smokers [%]	48.3	57.5	
Current smokers 1-34 cigarettes/day [%]	19.0	12.9	
Current smokers 35+ cigarettes/day [%]	4.1	6.0	
Alcohol consumption			
Frequency [times/month¶], mean (SE)	15.6 (1.89)	9.5 (1.25)	0.02‡
Frequency [times/month¶], median	0.85	0	
Alcohol intake [g/d#], mean (SE)	11.1 (1.19)	7.0 (1.60)	0.02‡
Alcohol intake [g/d#], median	0	0	
Race/ethnicity			
Non-Hispanic White [%]	85.9	86.2	0.17§
Non-Hispanic Black [%]	6.9	7.5	
Mexican-American [%]	1.9	3.7	
Others [%]	5.5	2.6	
Physical activity			
Moderate & vigorous** [times/week], mean (SE)	6.90 (0.35)	5.97 (0.63)	0.24‡
Moderate & vigorous** [times/week], median	5.23	4.11	
Vigorous†† [times /week], mean (SE)	3.58 (0.26)	3.18 (0.35)	0.46‡
Vigorous†† [times /week], median	0.42	0.75	

* All percentages and means are calculated using sampling weights; adjusted for age
† SE, standard error of the mean
‡ t-test
§ chi square test
¶ assessed by food frequency questionnaire during the household interview
# assessed by a 24-hour recall during the physical examination
** *Moderate activity* = walking, jogging or running, biking, swimming, aerobics, dancing, calisthetics, gardening, lifting weights, other physical activity if MET-h > 2.4 (if age 60-64), if MET-h > 1.9 (if age 65-79), or if MET-h > 1.25 (if age > 79)
†† *Vigorous activity* = walking (if age > 79), jogging or running, biking (if age > 64), swimming, aerobics, dancing (if age > 64), calisthetics (if age > 64), gardening (age > 64), lifting weights (if age > 79), other physical activity if MET-h > 5.9 (if age 60-64), if MET-h > 4.7 (if age 65-79), or if MET-h > 2.9 (if age > 79)

TABLE 2. Odds ratios* of LUTS by cigarette current smoking status and by pack-years of smoking in male NHANES III participants 60 years and older, 1988-1994

	Cigarette smoking status			
	Never	Former	Current, 1-34 cigarettes per day	Current, 35+ cigarettes per day
OR†‡ (95% CI)	1.00	1.46 (0.88, 2.40)	0.84 (0.46, 1.54)	1.83 (0.74, 4.53)
OR§ (95% CI)	1.00	1.37 (0.79, 2.36)	0.78 (0.39, 1.56)	0.75 (0.31, 1.82)
	Pack-years of cigarette smoking			
	Never	<21	21-49.9	50+
All men				
OR‡ (95% CI)	1.00	1.27 (0.78, 2.04)	1.10 (0.66, 1.83)	1.72 (0.99, 2.99)
OR§ (95% CI)	1.00	1.22 (0.69, 2.14)	1.22 (0.68, 2.19)	1.43 (0.80, 2.59)
Current smokers only				
OR‡ (95% CI)	1.00	0.52 (0.14, 1.91)	1.08 (0.50, 2.32)	1.19 (0.55, 2.56)
OR§ (95% CI)	1.00	0.64 (0.13, 3.06)	0.78 (0.25, 2.44)	1.08 (0.44, 2.65)
Former smokers only				
OR‡ (95% CI)	1.00	1.34 (0.82, 2.20)	1.07 (0.59, 1.94)	2.16 (1.12, 4.17)
OR§ (95% CI)	1.00	1.21 (0.65, 2.25)	1.22 (0.64, 2.31)	1.91 (0.97, 3.78)

*All results were calculated using sampling weights

† OR = odds ratio, CI = confidence interval

‡ adjusted for age and race

§ adjusted for age, race, frequency of moderate and vigorous physical activity, frequency of alcohol consumption, current waist circumference (continuous)

TABLE 3. Odds ratios* of LUTS by frequency of alcohol consumption in male NHANES III participants 60 years and older, 1988-1994

	Alcohol consumption [frequency]				
	Never	Up to once per week	More than once per week but less than daily	At least once per day	p-trend
OR†‡ (95% CI)	1.00	0.60; 0.33-1.09	0.74; 0.37-1.45	0.59; 0.36-0.97	0.08
OR§ (95% CI)	1.00	0.53; 0.24-1.18	0.99; 0.47-2.08	0.59; 0.34-1.03	0.25

*All results were calculated using sampling weights

† OR = odds ratio, CI = confidence interval

‡ adjusted for age and race

§ adjusted for age, race, frequency of moderate and vigorous physical activity, frequency of alcohol consumption, current waist circumference (continuous)

TABLE 4. Odds ratios* of LUTS by frequency of moderate and/or vigorous physical activity in male NHANES III participants 60 years and older, 1988-1994

	Moderate† and vigorous‡ (times per week)				
	0	0.1-3.0	3.1-6.0	>6.0	p-trend
OR§¶ (95% CI)	1.00	0.48 (0.24, 0.99)	0.41 (0.18, 0.91)	0.49 (0.29, 0.84)	0.05
OR# (95% CI)	1.00	0.32 (0.14, 0.74)	0.23 (0.09, 0.57)	0.35 (0.18, 0.67)	0.07
	Vigorous activity‡ (times per week)				
	0	0.1-2.0	2.1-4.0	>4.0	p-trend
OR¶ (95% CI)	1.00	0.52 (0.25, 1.10)	0.85 (0.40, 1.82)	0.80 (0.46, 1.40)	0.88
OR# (95% CI)	1.00	0.36 (0.15, 0.87)	0.78 (0.32, 1.88)	0.77 (0.37, 1.60)	0.80

* All results were calculated using sampling weights

† *Moderate activity* = walking, jogging or running, biking, swimming, aerobics, dancing, calisthetics, gardening, lifting weights, other physical activity if MET-h > 2.4 (age 60-64), if MET-h > 1.9 (age 65-79) or if MET-h > 1.25 (age > 79)

‡ *Vigorous activity* = walking (age > 79), jogging or running, biking (age > 64), swimming, aerobics, dancing (age > 64), calisthetics (age > 64), gardening (age > 64), lifting weights (age > 79), other physical activity if MET-h > 5.9 (age 60-64), if MET-h > 4.7 (age 65-79) or if MET-h > 2.9 (age > 79)

§ OR = odds ratio, CI = confidence interval

¶ Adjusted for age and race

Adjusted for age, race, current waist circumference, frequency of alcohol consumption, and cigarette smoking

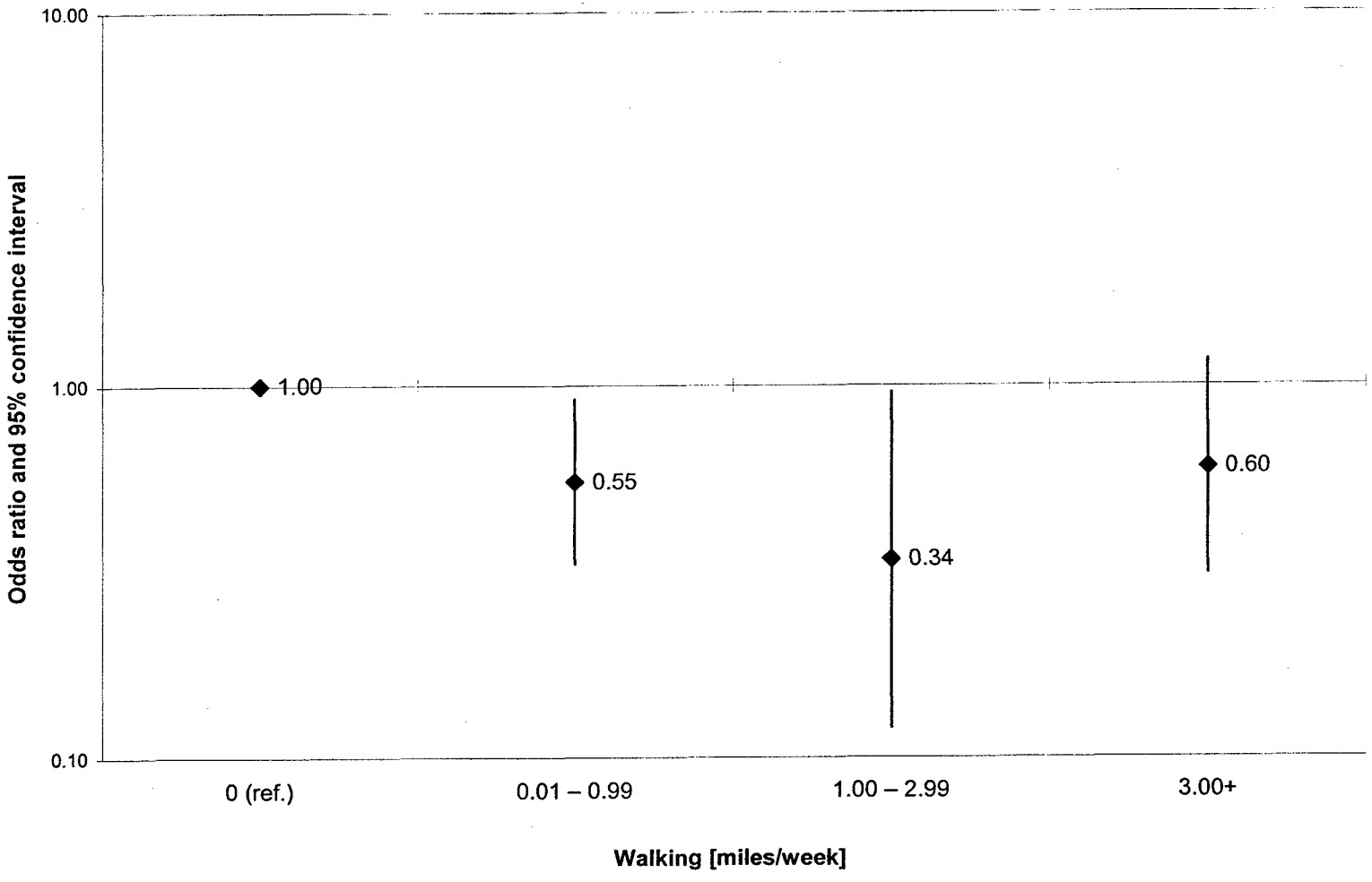
10.00
1.00
0.10
Odds ratio and 95% confidence interval
1.00
0.55
0.34
0.60
0 (ref.)
0.01 – 0.99
1.00 – 2.99
3.00+
Walking [miles/week]

FIGURE 1. Age- and race-adjusted odds ratio of LUTS by walking (miles per week) in male NHANES III participants, aged 60 years and older, 1988-1994

Crespo CJ, Garcia-Palmieri M, Smit E, McGee D, Lee IM, Balderrama F, Sorlie P.
Title: Physical inactivity is not a predictor of prostate cancer in Puerto Rican men.
Purpose: to study the effect of physical inactivity on prostrate cancer mortality among Puerto Rican men.
Methods: This study uses an observational cohort study of randomly selected sample of 9,824 men aged 35-79 years at baseline (1964) who were part of the Puerto Rico Heart Health Program (PRHHP) with follow up until 2002. The participants took part in multiple examinations including extensive information on lifestyle, diet, body composition, exercise, and smoking habits. The relationship between prostrate cancer mortality and physical activity status assessed using Framingham Physical activity Index which assesses occupational, leisure-time and other physical activities measured as usual activity over the course of a 24-hour day. The number of hours at each activity was converted to an index of usual daily energy expenditure, ranging between 24 and 71, and by grading activities into different categories using MET values. Physical activity was stratified into quartiles. Quartile 1 included those as doing nothing or very slight activities as sitting, and quartile 4 were the most physically active. Prostate cancer mortality was ascertained using death certificate information.
Results: The age adjusted estimates for prostate cancer mortality of each quartile of physical activity, taking Q1 as reference category, were Q2 OR = 1.23, CI 95% 0.65 – 2.33; Q3 OR = 1.31, CI 95% 0.73 – 2.37; and Q4 OR = 1.30, CI 95% 0.62 – 2.08. Thus, physical activity was not a predictor of prostate cancer mortality in this group of Puerto Rican men.
Conclusion: Our finding support that there is no relation between physical activity and prostrate cancer mortality in the longitudinal cohort study of Puerto Rican men